Changing dynamics of invasive meningococcal disease in the UK following the introduction of the novel 4CMenB vaccine

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PhD 2020

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A thesis submitted in partial fulfilment of the requirements of Manchester Metropolitan University for the Degree of Doctor of Philosophy by Published Work (Route 2)

Faculty of Science and Engineering in the Department of Life Sciences
Manchester Metropolitan University 2020

Acknowledgements

I would like to thank Dr Gayatri Amirthalingam who first invested, encouraged and guided me through much of this journey, both personally and professionally. There are a number of colleagues who have not only helped me during the past five years but have also showed me what it takes to build and sustain the amazingly successful national immunisation programme we have in England. Professor Mary Ramsay, Professor Nick Andrews and Dr Sema Mandal, all of whom I am in awe of their passion, commitment and expertise. I will always be eternally grateful for the help, time and patience provided by Sonia Ribeiro and Kazim Beebeejaun, they taught me how data should be approached. My MRU colleagues are scientists I also have an incredible amount of respect for, Professor Ray Borrow, Dr Jay Lucidarme, Dr Steve Gray and Dr Stephen Clark, thank you for always answering my seemingly endless laboratory based questions and supporting me in any attempts to deepen my understanding of the many complex things you do.

None of this work would have been possible without my co-authors, whose hard work, time and technical expertise are the reason the eight papers comprising this thesis, are what they are. Dr Helen Campbell has been my biggest support over the past few years, consistently, but especially when times became particularly trying for me personally. I can never really express my gratitude. Dr Shamez Ladhani, is and will always be someone who I have an immense respect for and owe this entire opportunity to. Thank you for your encouragement, your constant belief in me as a scientist and the countless amount of great talks we've had over the past few years. My gratitude also goes to Professor Kath Whitehead, thank you for agreeing to supervise me, your honesty, input and critiques have been invaluable.

To friends who have grown to feel like family, Alina and Aash, you've both been there for me unwaveringly, without judgment and always ready with words of encouragement. You're both rocks and feel more like sisters than friends, thank you for all the support and laughs, I'm endlessly grateful.

Most importantly, to my parents, Jan and Sid, I am everything I am and have all I have because of your sacrifices and every piece of guidance you've given me. Making you proud is a big driving factor behind all I do. To my brother Shea, you are my greatest inspiration, thank you so much for loving me enough to always push me to be better, for challenging the parameters of my comfort zone and striving to understand me, even when our differences can at times seem polar. To the three of you, this is my achievement, as much as it is collectively yours.

Contents

Abbreviations

4CMenB	Four-component capsular group B meningococcal vaccine (Bexsero)
aHUS	Atypical haemolytic uremic syndrome
cc	Clonal complex
CHIS	Child Health Information Systems
COVER	Cover of Vaccination Evaluated Rapidly
CSF	Cerebrospinal fluid
fHbp	Factor H-binding protein
GWAS	Genome wide association study
HPT	Health Protection Team
IMD	Invasive meningococcal disease
IRR	Incidence rate ratio
MATS	Meningococcal Antigen Typing System
MenB	Group B Neisseria meningitidis
MenC	Group C Neisseria meningitidis
MenW	Group W Neisseria meningitidis
MenY	Group Y Neisseria meningitidis
MeNZB	New Zealand OMV vaccine
MLEE	Multilocus enzyme electrophoresis
MLST	Multilocus sequence typing
MRU	Meningococcal Reference Unit
NadA	Neisseria adhesin A
NHBA	Neisserial heparin-binding antigen
NHS	National health service
OMV	Outer-membrane vesicle
ONS	Office of National Statistics

PBT	Positive bactericidal threshold
PCR	Polymerase chain reaction
PCV	Proportion cases vaccinated
PDS	NHS Personal Demographic Service
PHE	Public Health England
PMC	Primary meningococcal conjunctivitis
PorA	Porin A
PPV	Proportion population vaccinated
RP	Relative potency
ST	Sequence type
VE	Vaccine effectiveness
VR	Variable region

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Abstract

The epidemiology of infectious diseases must consider a number of aspects of the disease along with its control and prevention, as these will ultimately alter disease incidence, trends and distribution within a population. For many infectious diseases, the greatest medical tool available to combat them is vaccination. Historically, the UK has successfully controlled invasive meningococcal disease through vaccination. As a result, the majority of disease seen in today's epidemiological landscape is caused by a previously non-preventable form. Monitoring the epidemiology of invasive meningococcal disease relies on strong surveillance systems which in turn, allow for the evaluation of vaccination programmes. An understanding of the relationship between a vaccination programme and its effect on the epidemiology of the targeted disease is vital for assessing the success of a programme and gives insight into how these programmes may be improved.

This thesis presents eight studies, presented in three sections, that used epidemiological data to demonstrate the success of the national infant MenB vaccination programme in England. The studies presented have provided baseline estimates of the burden of invasive meningococcal disease (IMD) and the predicted strain coverage of the 4CMenB vaccine against circulating strains in England prior to the vaccine's national introduction in September 2015. These studies also provided the first ever estimates of 4CMenB's vaccine effectiveness at a reduced vaccination schedule, to that used for licensure, along with the impact on MenB disease in the group with the highest incidence of disease, children under the age of five, who were targeted with the vaccine. Further, these studies looked at the epidemiology and trends of disease in vulnerable populations in England, highlighting the markedly increased risk in a young person on long term complement inhibitor therapy and raising awareness of the increased risk in cases who initially present with a less common presentation and its implications for the public health and clinical management of these cases. Finally, these studies explored cases of IMD in pregnant women in England over a four-year period and showed that while disease during pregnancy can be severe, there was an unusual

finding of a significantly decreased risk of IMD in pregnant women compared to non-pregnant women of a similar age.

The combined findings of these studies show the success of the first nationally funded 4CMenB immunisation programme and its subsequent effects on the epidemiology of invasive meningococcal disease in England.

Chapter One

Understanding the epidemiology of communicable diseases encompasses multiple factors rooted in its aetiology. Understanding how patterns of how a pathogen acts, how the human body responds, and the pathogen's behavior once it has successfully infected a population are all required to successfully control and prevent its spread. High quality, multifaceted surveillance underpins all of those aspects and is pivotal in implementing disease control programmes. Invasive meningococcal disease (IMD) is a severe disease which is marked by its rapid and aggressive nature which can be life-threatening and many survivors are left with long-term complications which include amputations, deafness and neurological complications. While IMD is rare in the UK, the highest burden falls on children aged under five years, particularly in infants, with a second peak in incidence in adolescents and older adults aged 65 and older. In the UK the highest burden of IMD is due to a type of meningococci that until 2013 was previously unpreventable. A novel multicomponent vaccine, 4CMenB, prevents this form of disease and was licensed on immunogenicity studies alone. In September 2015, the UK was the first country to introduce this vaccine into its nationally funded infant immunisation programme.

1. Neisseria meningitidis

The meningococcus

Known scientifically as *Neisseria meningitidis*, the meningococcus is the organism responsible for invasive meningococcal disease (IMD). *N. meningitidis* is a member of the Neisseriaceae bacterial family, is a Gram-negative ß-proteobacterium, and is a fastidious facultative anaerobe, meaning that it can grow with or without the presence of oxygen. It is exclusively found in humans where its main reservoir is the nasopharyngeal tract and is typically harmless (Van Deuren et al., 2000). As a result, it is often considered an 'accidental pathogen' that harbors a number of characteristics which help it survive and invade host tissues.

The polysaccharide capsule

Meningococci can be encapsulated or unencapsulated, although the vast majority of bacteria responsible for causing invasive disease, when they enter normally sterile sites such as blood or cerebrospinal fluid (CSF), are encapsulated. The bacterial capsule is composed of polysaccharides, and those associated with the main bacterial type associated with invasive meningococcal disease (IMD) are usually composed of sialic acid derivatives. The exception to this are MenA and MenX organisms whose capsules are comprised of repeating units of N-acetyl-mannosamine-1-phosphate (Swartley et al., 1998). Neu5Ac is the most common form of sialic acid in humans and plays an important role in intracellular/intramolecular recognition (Varki et al., 2017). Neu5Ac is incorporated into the capsule of the meningococcus and this molecular mimicry allows it to be less detectable to the host's immune system (Rouphael and Stephens, 2012). One example can be seen in the MenB capsule, which contains a form of sialic acid (α (2-8)-linked homopolymer) which is identical to human fetal neuronal cell adhesion molecules (Rouphael and Stephens, 2012). This makes it a challenging to target the MenB capsule in vaccines as it runs the risk of eliciting an autoimmune response.

The biochemistry of the capsule is the foundation for the categorisation and nomenclature of the *N. meningitidis* bacterial species which is referred to as the serogroup. Based on antigenic differences in the polysaccharide capsule, there are 12 serogroups, A, B, C, E, H, I, K, L, X, W, Y and Z. Half of these (A, B, C, W, X, and Y) are responsible for the majority of IMD, with prevalence of each varying greatly by geographic region.

The polysaccharide capsules of B and C organisms are composed of entirely sialic acid with MenB and MenC having α 2>8 and α 2>9 linkages respectively (Table 1). MenW contains repeating units of sialic acid and D-galactose while MenY is comprised of sialic acid and D-glucose. MenA and MenX capsules do not contain sialic acid and instead are comprised of N-acetylmannosamine-1-phosphate and N-acetylglucosamine-1-phosphate respectively (Table 1). Thus, the polysaccharide capsule helps to inhibit phagocytosis and provides resistance to antibody/complement-mediated killing

(Kugelberg et al., 2008) and thus is essential for bacterial survival in blood and is also involved in the bacteria's propensity to cause disease, in immunocompetent individuals.

Table 1: Comparison of important meningococcal serogroups and their capsule structures

Serogroup	Capsule structure		
A	Non-sialic acid capsule	Homopolymers of *N*-acetyl-D-mannosamine-1-*P*	(a1-6)-linked-*N*-acetyl-mannosamine-1-phosphate
X			(a1-6)-linked-*N*-acetyl-mannosamine-1-phosphate
B	Sialic acid capsule	Homopolymers of sialic acid	(a2-8)-linked-*N*-acetyl-neuraminic acid
C			(a2-9)-linked-*N*-acetyl-neuraminic acid
W		Heteropolymers of sialic-acid-containing diasaccharides	(a 2-6)-linked-6-D-Gal(a1-4)-*N*-acetyl-neuraminic acid
Y			(a 2-6)-linked-6-D-Glc(a1-4)-*N*-acetyl-neuraminic acid

Virulence

As *N. meningitidis* is a commensal bacterium it is commonly carried asymptomatically, in the mucosa of the nasopharynx, by approximately 10 % of the population (Caugant and Maiden, 2009). The rates of bacteria carriage increase in certain conditions, such as in those who have chronic upper respiratory conditions and those who smoke with peak carriage rates seen in adolescence. To be able to cause invasive disease, the bacterium must survive in the bloodstream and spread. In order for the meningococcus to survive, a number of different methods may be used to evade the host's immune

system. The ability for meningococci to cause disease relies on a combination of genes or allelic variants of genes (Tinsley and Nassif, 2001). There have been and continue to be multiple attempts to identify genetic elements of the bacteria that are associated with invasive disease (Tinsley and Nassif, 1996; Bart et al., 2000). To date the region in the bacteria which encodes the ability to synthesise the polysaccharide capsule remains the principal determinant of virulence (Caugant and Maiden, 2009). During pathogenesis, the expression of the polysaccharide capsule undergoes genetic regulation (Pizza and Rappuoli, 2015). The meningococcal capsule is essential for survival in the blood as it prevents phagocytosis and aids in the evasion of the host's immune response. For this reason, the genes responsible for capsular synthesis, termed *cps* are typically upregulated when invading the bloodstream and downregulated or lost entirely during asymptomatic carriage (Pizza and Rappuoli, 2015). This, along with a number of other factors result in meningococci having a pathogenic potential with the ability to pass through epithelial cells and enter the blood stream where they may survive and multiply (Taha et al., 2002; Caugant and Maiden, 2009). The bacterial capsule offers protection from the host's immune system as it is poorly immunogenic and along with other surface structures of the bacteria, such as those involved in attachment to host cells or those that can stimulate the release of inflammatory mediators can lead to septic shock (Van Amersfoort et al., 2003).

Many meningococci do not have capsular loci, cannot generate a capsule and are not associated with invasive disease in healthy individuals as they are killed by complement (Jódar et al., 2002). It is known that meningococci can switch their capsular expression in the nasopharynx (Ala'Aldeen et al., 2000) and thus a hypervirulent MenC strain has the potential to become a hypervirulent MenW strain thereby potentially evading vaccine-induced immunity (Lucidarme et al., 2017).

Pathogenesis

Invasive meningococcal disease occurs when the meningococcus enters an otherwise sterile site in the body (such as blood, CSF, joint fluids) which can result in meningococcemia, meningitis, septic arthritis, septic shock, purpura fulminans,

pneumonia, arthritis, epiglottitis and pericarditis (Harfi et al., 2012). Although rare, IMD is a life-threatening disease and one that is feared due to its sudden onset and rapid deterioration. Case fatality rates of up to 80% have been seen in untreated cases (Flexner, 1913) and 8-15% in those receiving treatment (ECDC, 2017b). Survivors of IMD may also experience marked morbidity with 12-20% suffering from clinical sequelae such as deafness, brain damage and amputations (Lucas et al., 2016).

2. Risk factors for IMD

Host factors

IMD is typically a disease of healthy individuals, although the exact reasons as to why some people develop more severe disease than others are still not fully understood. Recent studies using genome wide association studies (GWAS) (Davila et al., 2010) have identified aspects within hosts that may contribute to an increased susceptibility to IMD. One interaction which has proven to be important in the pathogenesis of IMD is that between the meningococcus and the complement system (Ladhani et al., 2019) In immunocompetent individuals, their complement system acts as a first line of defense against IMD, as it is essential in lysing the bacteria in the blood (Lewis and Ram, 2014; Ladhani et al., 2019). Therefore, in individuals with defects in various components of the complement system; such as in the alternative pathway (properdin and factor D), the terminal pathway (C5 to C9) (Rosain et al., 2017) as well as those with autosomal recessive terminal complement pathway deficiencies are all at an increased risk for IMD (Figueroa et al., 1993).

In addition to inherited complement deficiencies, there are also medical conditions and treatments, particularly those for paroxysmal nocturnal haemoglobinuria (PHN) and atypical haemolytic uraemic syndrome (aHUS), that require complement inhibitors which in turn can result in either acquired or secondary complement deficiency (Figueroa and Densen, 1991). Individuals with these disorders are rare (0.03% of the general population) but are associated with a 7000 to 10,000-fold higher risk of IMD, with 50-60% experiencing ≥1 IMD episode (Figueroa and Densen, 1991). Other

immunocompromised individuals such as those with human immunodeficiency virus (HIV) have also been associated with an increased risk for IMD (Simmons et al., 2015). A family history of IMD has been shown to be associated with an increased risk which would suggest there may be genetic factors that may be important for susceptibility to this disease (Olea et al., 2017). A case-control study showed genetic polymorphisms may effect susceptibility to IMD (Domingo et al., 2002) while population-based methods, such as genome-wide association studies (GWAS) have shown genetic variation in the complement factor H (CFH) is associated with susceptibility to IMD (Davila et al., 2010). GWAS studies of meningococcal cases has shown that variation in the regulation of complement activity plays a role in determining which individuals will get invasive disease versus those who will be asymptomatic carriers (Davila et al., 2010; Martinón-Torres et al., 2016).

Environmental factors

The environmental factors that contribute to a higher chance of developing IMD are those associated with settings that increase the chance of an individual encountering and acquiring meningococci. These settings include crowding in both living and social situations, mixing of adolescents in university halls of residence (Mandal et al., 2017), crowded conditions associated with mass gatherings such as Hajj, the annual Islamic pilgrimage to Mecca (Yezli, 2018) and other international mass gatherings, such as music festivals, scout jamborees (Kanai et al., 2017) and more recently, funerals (Patel et al., 2017). Seasonal changes are also highly associated with IMD incidence. In temperate climates, such as in England and mainland Europe, peak incidences are seen in the winter months. This could be for a number of reasons, including an increased tendency to spend time indoors along with a simultaneous increased incidence for viral infections, where influenza in particular has been shown as a risk factor for IMD(Cartwright et al., 1991; Jacobs et al., 2014). Conversely, the dry season is often the peak of IMD incidence in sub-Saharan Africa where dust and low humidity are the environmental conditions thought to be linked to this spike in IMD incidence (Palmgren, 2009).

3. Methodologies in the characterisation of *N. meningitidis*

Serogroup typing

Classification by serogroup is extremely useful and often the first method of summarising IMD epidemiology. However, a deeper understanding of IMD epidemiology and potential methods of prevention through vaccination requires knowledge beyond serogroup (Harrison et al., 2009). Newer molecular approaches to IMD classification accompany the traditional serological methods to help scientists better understand trends of IMD and how meningococci may be changing over time.

PCR

Since the mid-1990s PCR-based diagnostics have been more widely used to identify patients with meningococcal disease as well as other bacterial infections (Corless et al., 2001). Since its introduction this diagnostic method has substantially increased IMD burden estimates (Gray et al., 2006). A negative aspect of PCR is the absence of a bacterial isolate for phenotyping. Phenotyping allows for a finer level of classification, beyond capsular group and subtype. However, there are further genotypic characterisations possible from PCR samples.

Multilocus sequence typing

Since its introduction in 1998 multilocus sequence typing (MLST) has become more widely used for the molecular characterisation of *N. meningitidis*. MLST is a nucleotide sequence-based approach that can be applied to many bacterial pathogens and is conducted by sequencing bacteria's DNA on seven portions of the DNA known as 'housekeeping genes'. The reason housekeeping genes are the focus of this method is because these genes are not considered to be under any selective pressure. This results in allelic profiles of isolates that can be compared to a large central database and used to determine the genetic lineage of *N. meningitidis* (Maiden et al., 1998). Another advantage of MLST is that allelic profiles can be obtained from clinical material. The seven housekeeping loci can be amplified in these samples directly from blood or

CSF from IMD cases by polymerase chain reaction (PCR) (Urwin and Maiden, 2003). This means isolates can be characterised even if they cannot be cultured from clinical specimens (Urwin and Maiden, 2003). MLST has widely replaced multilocus enzyme electrophoresis (MLEE) as the primary method for determining genetic lineage(Harrison et al., 2009). MLST targets the housekeeping genes to classify meningococci into sequence types (ST) based on changes in these genes. Meningococci are highly variable, but often the same ST can be found in different capsular groups, for example ST-11 clonal complex (cc11; also known as the ET-37 complex and lineage 11) are hyperinvasive and may express serogroups C or W and, less frequently, B or Y (Lucidarme et al., 2015). Beyond this, meningococci are often also classified by clonal complexes (cc), bacterial lineages, which consist of groups of related STs. A clonal complex includes several lineages of highly related isolates (clones) (Taha, 2002). Most invasive meningococcal isolates belong to a limited number of ccs, which correspond to the hyperinvasive lineages (Lucidarme et al., 2015). The ability of a few hyper virulent meningococcal strains to cause the majority of disease globally is still not fully understood.

Whole genome sequencing

Whole genome sequencing (WGS) is newer approach of typing that offers an even higher resolution of characterisation, distinguishing meningococci on up to 2200 genes (Jolley et al., 2012). This also allows WGS to distinguish between very closely related meningococci and track the evolution of different strains (Whaley et al., 2018). In England, WGS has been routinely carried out on all bacterial isolates, which are those cases confirmed by culture where a live organism was isolated from a sterile site. Like MLST, databases have been developed to contain global genetic data from meningococcal WGS which enables the ability to map the distribution of isolates from across the world (Maiden et al., 1998).

Latex agglutination

Some countries use other non-culture based approaches to supplement cultures. These methods include Latex agglutination, a laboratory method used to check for certain

or antigens in a clinical specimens (typically blood or CSF). The sample is mixed with latex beads, coated with a specific antibody or antigen and if the suspected substance is present, the latex beads will clump together (agglutinate) (*Latex agglutination test: MedlinePlus Medical Encyclopedia*, n.d.). This allows for serogroup identification and is a rapid diagnostic with results taking from 15 minutes to an hour (Sobanski et al., 2001).

4. Epidemiology of IMD

IMD is a global disease and varies by serogroup, serotype, serosubtype, cc, geographical region and time. Patterns of IMD are unpredictable differing widely by age serogroup and severity. The majority of IMD is due to clonal complexes of *N. meningitidis* that harbor the propensity to emerge, spread and cause infection worldwide. MenC and MenW account for substantial proportions of IMD in most of Africa and Latin America, while MenB is the predominant serogroup across Europe, North America and the Western Pacific (Booy et al., 2018). While natural fluctuations in disease do occur, such trends are also influenced by public health interventions, including prevention and control through vaccination which will inevitably cause additional shifts in IMD epidemiology.

Understanding the local epidemiology, trends over time and impact of meningococcal vaccination programmes is important not only in understanding how vaccination programmes affect disease patterns but also to identify knowledge gaps and potential for further reductions in disease burden through additional preventive strategies as new more effective and higher valent meningococcal vaccines become available.

Epidemiology of IMD in England prior to September 2015

Trends in IMD across England and Wales have been consistently reported since the early 1990s. Data from the national reference laboratory between 1993/94 and 2003/04 reported an average annual incidence of 3.8/100,000 population (median: 3.8/100,000; range: 2.3-5.4/100,000) (Gray et al., 2006). This also captured the start of an increase in MenC disease in 1995/96 with continued momentum and associated increase in mortality through 1999/00. This finding lead to widespread introduction of the meningococcal group C conjugate (MCC)

vaccine in November 1999 for all individuals aged less than 25 years of age. The introduction of the MCC vaccine was based on serological criteria alone, without the direct evidence of vaccine efficacy which set a precedent for other meningococcal vaccines (Miller et al., 2001). Between 1993/94-2000/01 a continued increase in MenB incidence was observed along with their diversity in phenotypes where it accounted for the majority of disease but at that time was unpreventable. Since 2009/10, the UK has experienced a year-on-year increase in MenW disease due to rapid expansion of a single endemic hyper-virulent strain belonging to sequence type 11 clonal complex (cc) (Ladhani et al., 2015). Consequently, the quadrivalent MenACWY conjugate vaccine was introduced in adolescents aged 13-18 beginning August 2015 (Campbell et al., 2015). It was recently reported that serum samples from children immunized with a meningococcal serogroup B vaccine (4CMenB) demonstrated potent serum bactericidal antibody activity against the hypervirulent *Neisseria meningitidis* serogroup W strain belonging to the sequence type (ST) 11 clonal complex, circulating in England (Ladhani et al., 2016).

5. Meningococcal vaccines

Vaccination is the key method of IMD prevention with various vaccines and vaccination strategies developed over the years. Vaccination aims to protect those who are vaccinated against IMD when exposed as well as reducing the acquisition, carriage and onward transmission of the bacteria (Borrow et al., 2017).

Polysaccharide vaccines

Polysaccharide vaccines containing the polysaccharide capsule of single or multiple meningococcal serogroups have been available for more than 40 years. While they remain ineffective in young children, they have been proven to be immunogenic and safe in older children and adults. Most polysaccharides are thymus-independent antigens which do not require T-cells to induce an immune response (Mond et al., 1995). This often results in them being unable to induce memory cells in neonates and infants and, therefore, have a short duration of protection and poor responses to

booster doses (Ali et al., 2014). Polysaccharide vaccines are still used, mainly in lower- and middle-income countries (LMICs), due to their low cost (Vaughan et al., 2019).

Conjugate vaccines

Protein-conjugate vaccines, on the other hand, use a carrier protein to present the meningococcal capsular polysaccharide to the immune system, in a manner that induces a T-cell mediated response (Ali et al., 2014). As a result, these vaccines are immunogenic from birth, induce immune memory, protect for a longer duration and provide a booster response with subsequent doses (Borrow et al., 2017). In addition to providing direct protection in vaccinated individuals, protein-conjugate vaccines also prevent the acquisition of bacterial carriage, thus disrupting transmission and inducing indirect (herd) protection across the population (Trotter and Maiden, 2009). Currently, both polysaccharide and protein-conjugate vaccines are available against serogroups A, C, W and Y; since these vaccines contain capsular antigens, they do not provide cross-protection against other meningococcal serogroups. Similar protein-conjugate vaccines against MenB have been difficult to develop because the MenB capsular polysaccharide contains components which are similar to human foetal neuronal cells and are, therefore, poorly immunogenic with the potential to induce autoimmune antibodies (Tan et al., 2010).

Outer membrane vesicle vaccines

Meningococcal outer membrane proteins have been used for over 20 years in millions of vaccine doses. They have been used as a carrier protein in *Haemophilus influenzae* type b (Hib) polysaccharide conjugate vaccine and as vesicle vaccine formulations against meningococcal disease (Holst et al., 2009). In Gram negative bacteria, outer membrane vesicles (OMVs) play a key role in the interaction and communication between the host and pathogen (Vernikos and Medini, 2014). OMVs are involved in overall disease progression, since they act as vehicles for the secretion of bacterial proteins and lipids which allows them to play a role in colonization, modification of the host's immune response and delivery of virulence factors into host cells (Kuehn and Kesty, 2005). Research into the use of OMV based vaccines to control specific

outbreaks began in the 1970s and since then there have been three independently developed vaccines for the use against regional MenB outbreaks in Cuba (1987-1989), Norway (1988-1991) and New Zealand (2004-2008), with estimated vaccine effectiveness of 83%, 87% and 73% respectively (Sierra et al., 1991; Rosenqvist et al., 1995; Arnold et al., 2011). The compromise with OMV vaccines is the tradeoff between their coverage and effectiveness. Mounted immune responses by these vaccines are largely strain specific and directed against the immunodominant PorA in the vaccine. An exception to the typical homologous coverage was observed with two OMV vaccines. Cuba was the first to develop and successfully test the first effective MenB OMV vaccine (VA-MENGOC-BC) OMV vaccine that was used to control an outbreak of MenB (B4:P1.15) in both Cuba and Brazil, where it proved effective against both the outbreak strain and other circulating strains of MenB (Sierra et al., 1991; de Moraes et al., 1992). Similarly, the New Zealand OMV vaccine (MeNZB^{â}) seemed to be cross-protection between strains and regional evidence showed an estimated 54% effectiveness against heterologous MenB strains as well as 56% effectiveness against circulating non-MenB strains (Arnold et al., 2011).

Reverse vaccinology and 4CMenB

Reverse vaccinology uses a genomic, rather than cellular approach to vaccine development. Vaccines are classically developed using a pathogenic strain *in vitro* to produce a live attenuated strain that is harmless to the host but preserves its ability to elicit an immune response. Other approaches have also used antigens to develop subunit vaccines. These methods have been highly successful for a number of pathogens but remain unfeasible in cases where components of the pathogen, like MenB, that provoke immune responses are very similar to components in host tissues (Vernikos and Medini, 2014). Thus, reverse vaccinology has been applied successfully to pathogens that have otherwise been pervicacious. The first example of successful application of reverse vaccinology was the 4CMenB vaccine.

The 4CMenB vaccine

This first success in reverse vaccinology identified three recombinant proteins—factor H binding protein (fHbp) variant 1.1, neisserial heparin-binding antigen (NHBA) peptide 2, and neisserial adhesin A (NadA) variant 3. These three recombinant proteins were included in 4CMenB, together with outer membrane vesicles containing the porin PorA (P1.4) from a New Zealand outbreak strain used in MeNZB®.

These proteins are each involved in different processes of IMD pathogenesis. Factor H binding protein (fHbp) is a surface-exposed lipoprotein. Its function is to help the meningococcus evade alternative complement pathway-mediated killing by binding activate factor H onto the cell surface of the meningococcus (Madico et al., 2006)

Previously referred to as GNA2132, the neisseria heparin binding antigen (NHBA) is an important protective antigen of *N.* meningitidis. NHBA binds heparin and heparin sulphate which is thought to play a role in the evasion of complement-mediated bacterial lysis (Serruto et al., 2010). Neisserial adhesion A (NadA) is also a surface exposed protein that is believed to have a role in meningococcal adhesion to epithelial cells of the nasopharynx. Unlike capsular polysaccharides, which tend to be expressed abundantly and are antigenically relatively uniform in invasive meningococci, surface proteins can be sparse and antigenically diverse. This also means that the vaccine will not protect against all MenB strains.The ability of 4CMenB to protect against serogroup B meningococcal strains and the breadth of protection depends on the degree of surface expression and the extent to which vaccine induced antibodies recognise and bind to these proteins (Donnelly et al., 2010). To evaluate vaccine strain coverage, the Meningococcal Antigen Typing System (MATS) was created by the vaccine manufacturer. MATS was a novel laboratory testing method to be used on invasive isolates. It aimed to determine whether in the isolate, each antigen was sufficiently expressed and if the isolates antigen(s) was similar enough to the antigen in the vaccine such that antibodies elicited by 4CMenB would lyse the bacterium (Plikaytis et al., 2012).

6. Surveillance of IMD

Disease surveillance systems are the means by which the prevalence, incidence and distribution of IMD is ascertained. Differences in IMD epidemiology can only be fully understood in the context of a region's surveillance system and the associated strengths and weaknesses. The ideal system would have laboratory-based surveillance that confirms clinically suspected cases of IMD to inform national surveillance. Most surveillance systems rely on specimens from normally sterile sites (CSF, blood and other normally sterile bodily fluids) since specimens from non-sterile sites like the pharynx are not used to confirm invasive disease as a large proportion of the population asymptomatically carry *N. meningitidis* in this part of the body.

Incidence of IMD varies globally by region and in many areas of the world, the gold-standard method of active surveillance and laboratory confirmation and strain characterisation is not possible. Thus, combinations of different surveillance systems and diagnostic methods are used and vary by and across country, making comparison and ascertainment of true IMD incidence difficult.

The following sections focus on specific areas of surveillance that are used to derive data on IMD epidemiology and burden within a given population.

Sentinel surveillance

In addition to case ascertainment, population-based surveillance is ideal as it enables disease incidence to be determined (Harrison et al., 2009). This can be achieved through sentinel surveillance which uses nominated reporting units with a high probability of seeing cases of the disease in question (*WHO | Sentinel Surveillance*, n.d.). This can be useful if the population base is known and the chosen centres are thought to be representative of the general population. However, if this is not the case the incidence of IMD cases can be skewed or under-representative. However, when the chosen sites are applicable to the general population, sentinel surveillance can be very useful in determining disease incidence (Harrison et al., 2009).

Active or passive surveillance

Another feature of surveillance systems is whether they are active or passive. Passive surveillance often involves reporting of IMD cases, usually required by law, by healthcare providers and/or laboratories. These reports are then collected by local health authorities. Passive surveillance is advantageous as it occurs continuously and requires few resources but relies on a strong public health infrastructure and would potentially not capture those without access to health care. Conversely, active surveillance involves health authorities regularly contacting each entity required to report cases and eliciting reports (Harrison et al., 2009). The main difference between these methods is the sensitivity of surveillance (proportion of notifiable cases that are reported) is higher in active surveillance systems.

7. Surveillance of IMD in England

Notifications

Notification of clinically diagnosed cases of IMD, by a registered medical practitioner, is a statutory requirement in England and has been since the early 1990s where all cases of IMD require public health management. This is to ensure contacts of the case are identified and offered antibiotic chemoprophylaxis and vaccination (where appropriate) (PHE guidance 2019). This management is undertaken by the PHE Health Protection Teams (HPT) in an area local to the case. Medical practitioners responsible for the case notify their local HPT who then report this to PHE. As a result, there is a national record of notified cases captured on HPZone, a national web-based case management system used by local HPTs as a method to rapidly record public health events and actions. These notifications hold information on gender, age in years, regional location and often provide some insight into the clinical presentation of the case.

Laboratory confirmation of cases

When a high proportion of clinically suspected cases are investigated, microbiologically, laboratory confirmed cases offer a source of reliable surveillance data on a population

level. This data is both sensitive and specific and circumvents some of the uncertainty around diagnosis which is present for many diseases but especially IMD where initial presentations can often be non-specific(Gray et al., 2006). In England, the PHE Meningococcal Reference Unit (MRU) provides a national reference service for IMD confirmation and characterisation of invasive meningococci (both culture and non-culture). The MRU also provides free non-culture PCR confirmation of meningococcal diagnosis (including genogroup and genosubtype analysis) for clinical specimens from patients with suspected IMD, that are routinely submitted by the National Health Service (NHS) hospitals in England (PHE enhanced surveillance plan, 2019). Since 1999, all confirmed cases of IMD are referred to the PHE immunisation team where they are then followed up to confirm vaccination history, travel history, country of birth and any underlying medical conditions. Using laboratory confirmed cases to ascertain IMD incidence in England is a method that has proven high case ascertainment (Ladhani et al, 2015). Since July 2010, all invasive meningococcal isolates sent to the MRU are also whole genome sequenced.

Laboratory surveillance of MenB IMD

Invasive MenB disease is defined as an individual with isolation of MenB or positive capsular group B specific PCR from a normally sterile site. The impact of 4CMenB is monitored using the Meningococcal Antigen Typing MATS is not yet validated for use against non-MenB isolates.

The definition of an isolate with a positive MATS assay result ("MATS positive") and therefore potential coverage by 4CMenB is a MenB strain with a relative potency (versus that of a reference strain) of at least one vaccine protein (fHbp, NadA, NHBA) above the positive bactericidal threshold (PBT) and/or determination of a P1.4 PorA subtype by sequencing of VR2 and/or by serosubtyping.

In accordance with a new study (Muzzi et al., 2019) for non-culture MenB cases, a PorA genosubtype of P1.4 and /or fHbp genotype for peptides 1, 2, 4, 14, 15, 37, 89, 90, 110, 144, 224, 232, 245, 249, 252, or 510 are considered likely to be covered by the vaccine but this has not yet been validated against recent MATS data.

Vaccine coverage data

PHE routinely collects data on vaccine uptake using Collection of Vaccination Evaluated Rapidly (COVER), a mandated routine coverage collection which was established in 1987 COVER standardises on collecting data for children at 12 months, 24 months and 5 years of age. This is done through the collation of data from Child Health Information Systems (CHIS). Local authority data from CHIS are extracted to and submitted to PHE where they are collated and analysed to report on childhood vaccination levels in England.

Data on deaths

PHE has access to electronic death registration records provided by the Office for National Statistics (ONS). These are data where IMD, meningococcal septicaemia, meningococcal meningitis or other meningococcal related causes have been identified as the cause of death. ONS data is linked with laboratory data to determine casual capsular group of the infecting meningococci. Additionally, the NHS Personal Demographics Service (PDS) is also used to ascertain whether or not a patient has died within a reasonable period of disease onset (typically 28 days).

Enhanced surveillance in England

In 2013, PHE enhanced the laboratory surveillance of IMD by collecting clinical data using postal questionnaires to general practitioners (GPs) of laboratory confirmed IMD cases diagnosed since 01 January 2011. These questionnaires aimed to capture information on comorbidities, risk factors, clinical presentation, intensive care admission (ICU) and outcomes. Enhanced surveillance was revised to include an opportunity to collect vaccination history and extended to follow-up all laboratory confirmed cases of IMD from September 2015. Instead of requesting this information from GPs, enhanced surveillance from September 2015 involved the PHE immunisation team liaising with HPTs for the completion of epidemiological surveillance forms. In addition to these surveillance forms, detailed clinical questionnaires were designed for completion by the responsible hospital consultant for all cases of confirmed IMD in children less than 5 years of age. This questionnaire aimed to gather information on length of hospital stay,

clinical investigations including blood and cerebrospinal fluid test, imaging (CT scan, MRI or ultrasound), outcome and sequelae. Changes in the surveillance of IMD were made to align with the introduction of a new MenB infant vaccination programme and a MenACWY vaccination programme for teenagers.

From 1st of September 2015, all infants born on or after the 01 May 2015 were offered the vaccine at a reduced 2+1 schedule with two catch-up cohorts (Table 1).

Table 2: Definition of catch-up and routine cohorts eligible for Bexsero® under the national immunisation programme

Vaccination Cohort	Birth dates	Vaccination schedule
Catch-up cohort	May 2015	4 and 12-13 months (1+1)
	June 2015	3,4 and 12-13 months (2+1)
Routine cohort	on or after 01 July 2015	2,4 and 12-13 months (2+1)

This thesis presents eight studies to demonstrate the effect of the 4CMenB infant vaccination programme on the epidemiology of MenB disease in England and show that this work contributes the first real-world evidence of the vaccine's impact and effectiveness. This is split into three chapters in the form of: six observational studies, one case report, and one literature review from work carried out between 2015 and 2020 in England.

Chapter one begins with an overview of IMD, meningococcal vaccines, the development of vaccines against group B meningococcal disease, risk factors for disease and the types and roles of national surveillance in monitoring disease and vaccination programmes. Chapter two presents the first three studies which all explore a different

area of IMD epidemiology prior to the introduction of the new vaccine and how this provided a baseline for studies that came after its implementation. Chapter three is comprised of two studies that explain the epidemiological experience with the MenB vaccine in England, 10 months and 3 years after its introduction, and its effect and effectiveness in vaccinated populations. Chapter four contains three studies that examine IMD in vulnerable populations as what implications these risk factors have for the management of these cases. Finally, chapter five discusses the impact of the findings in the studies presented as well as potential for further work on group B meningococcal disease.

Chapter Two

1. Invasive meningococcal disease epidemiology and predicted strain coverage of 4CMenB prior to its introduction in the national immunisation programme in England

Critical account of published work on IMD epidemiology in England prior September 2015

Three publications have been selected that use national surveillance data to establish baselines, both epidemiological and molecular, against which the impact of the meningococcal group B vaccination programme will be measured in future. These studies updated and built on earlier epidemiological summaries conducted in England and Wales (Gray et al., 2006; Ladhani et al., 2012), along with strain coverage estimates (Vogel et al., 2013)and the potential of 4CMenB to protect against non-group B meningococcal strains (Ladhani et al., 2016).

3.1. Study 1

Epidemiology, clinical presentation, risk factors, intensive care admission and outcomes of invasive meningococcal disease in England, 2010-2015. *Vaccine* (2018)

Sydel R. Parikh, Helen Campbell, Stephen J. Gray, Kazim Beebeejaun, Sonia Ribeiro, Ray Borrow, Mary E. Ramsay, Shamez N. Ladhani

3.1.1. Study 1 Aim

This study aimed to summarise the epidemiology and capsular group distribution of IMD in England along with linked information on risk factors, clinical presentation and outcomes of disease over four calendar years. The study aimed to update national and regional incidences as well as exploring relationships between clinical presentations and outcomes.

3.1.2. Study 1 Summary

National surveillance data on laboratory confirmed cases of IMD along with capsular group, diagnostic method and regional information were used in conjunction with ONS data on population estimates to determine IMD incidence by age, capsular group and geographical region. Information from enhanced surveillance questionnaires sent to GPs included data on comorbidities, risk factors, clinical presentation, intensive care admission (ICU) and outcomes. Incomplete or missing information in the questionnaires was followed-up by telephoning the GP, contacting the patient's hospital clinician or requesting additional information from the local PHE health protection team (HPT), which maintains records of all suspected and confirmed IMD cases for public health management of cases and close contact and for monitoring outbreaks. If needed, additional information was sought from HPZone, electronic ONS death registration records were linked with laboratory data. Dates of death were confirmed using the NHS PDS and only deaths occurring within 28 days of receipt of sample were included. Clinical data were presented for cases diagnosed between January 2011and July 2015. These data were analysed descriptively and logistic regression was used where appropriate to investigate whether any associations between clinical and surveillance data existed.

3.1.3. Study 1 Results

This study provided updated and detailed insight into the burden of IMD in England between 2011-2015. This paper showed that IMD epidemiology in England was still similar to mainland Europe with declining incidences in both overall IMD and IMD due to MenB. The large cohort of cases allowed for the first time, the description of clinical presentations, risk factors, severity and outcomes of IMD by age and capsular group. England has one of the highest disease incidences in Europe and the resulting case numbers allow for a more accurate assessment of disease characteristics. Enhanced follow-up was achieved for all 3411 cases diagnosed in England during 01 January 2011 and 30 June 2015. Using this data, this study was able to show, for the first time, a low prevalence of known risk factors among IMD cases. This paper also presented data on a more detailed breakdown of disease in older age groups (>65 years). It was

interesting to note from this work that MenY cases became more prevalent with increasing age, as did atypical clinical presentations and diagnosis with only a cultured specimen.

3.1.4. Contribution to Study 1

Jointly conceived the project, solely carried out the data collation and analysis and wrote the first draft of the manuscript.

3.2. Study 2

Meningococcal serogroup B strain coverage of the multicomponent 4CMenB vaccine with corresponding regional distribution and clinical characteristics in England, Wales, and Northern Ireland, 2007–08 and 2014–15: a qualitative and quantitative assessment. ***Lancet Infectious Diseases*** **(2017)**

Sydel R. Parikh, Lynne Newbold, Stephanie Slater, Maria Stella, Monica Moschioni, Jay Lucidarme, Rosita De Paola, Maria Giuliani, Laura Serino, Stephen J Gray, Stephen A Clark, Jamie Findlow, Mariagrazia Pizza, Mary E Ramsay, Shamez N Ladhani, Ray Borrow

3.2.1. Study 2 Aim

This paper updated the predicted coverage of 4CMenB against circulating MenB strains in the UK, using MenB strains from two epidemiological years, 2007/2008 and 2014/2015. MATS coverage estimates were assessed for 2014-15 MenB isolates in the UK and then compared to corresponding 2007-08 data on MATS coverage estimates and regional distribution. An additional feature of this study was that it assessed age distribution, clinical characteristics and outcomes of IMD in patients with MATS-positive and MATS-negative MenB isolates in England. This estimate of coverage served as a baseline against which future estimates would be based following the introduction of the infant 4CMenB programme that commenced in September 2015 (data in this paper is to the end of June 2015).

3.2.2. Study 2 Summary

Invasive serogroup B meningococcal isolates from cases in England, Wales, and Northern Ireland were characterised genotypically by multilocus sequence typing (Jolley and Maiden, 2010) and each of the four main 4CMenB antigens. This was carried out

for two epidemiological years 2007-2008 and 2014-2015. Clinical characteristics, risk factors, and outcomes were assessed according to MATS coverage for 2014–15 English cases. In order to properly assess vaccine coverage estimates, it was necessary to determine the genetic constitution of the MenB isolates. This was conducted by characterising the genotypes of 2014–15 isolates with data extracted from the Meningitis Research Foundation's Meningococcus Genome Library was used since it contained the genome sequences for all English, Welsh, and Northern Irish invasive isolates received by the Public Health England Meningococcal Reference Unit since July, 2010. MATS data were generated for both epidemiological years (2007–08 and 2014–15) using the same methods described previously (Donnelly et al., 2010; Plikaytis et al., 2012; Domnich et al., 2015). PorA subtypes were determined by phenotyping. MATS predicted strain coverage was defined as the proportion of serogroup B meningococcal isolates with MATS relative potency greater than the positive bactericidal thresholds for one or more antigen or the presence of PorA (P1.4).

In 2014–15, 165 of 251 (66%; 95% CI 52–80) meningococcal group B isolates were estimated by MATS to be covered by 4CMenB, compared with 391 of 535 (73%; 95% CI 57–87) in 2007–08. The proportion of MATS-positive isolates with one vaccine antigen increased from 23% (122 of 535) in 2007–08 to 31% (78 of 251) in 2014–15, whereas the proportion with more than one antigen fell from 50% (269 of 535) to 35% (87 of 251). This effect reflected changes in the circulating strains, particularly the ST-269 clonal complex strains.

In a logistic regression model, MATS positivity was associated with a 1.95-fold increased risk (95% CI 1.02–3.76; p=0.017) of severe invasive meningococcal disease (intensive care admission, death, or both), independent of age, sex, underlying comorbidity, or clinical presentation.

3.2.3. Study 2 New knowledge gained

This study updated the predicted 4CMenB strain coverage for England, Wales and Northern Ireland prior to the introduction of the vaccine into the national immunisation programme in the UK. MATS coverage increased with age, varied by geographical region, and was associated with more severe disease. MATS coverage was highest for individuals older than 5 years for both 2007-08 (77%) and 2014-15 (70%). In 2014-15, MATS coverage as well as the number of antigens covered, were mostly lower across all age groups when compared with coverage estimates from 2007-08. Of particular interest, in 2014-15, over a third (37%) of MenB isolates in infants were MATS-negative and a further 30% were only covered by one vaccine antigen. MATS-positivity was also found to be associated with a significant 1.95-fold increased risk of severe IMD (intensive care admission, death or both) which was independent of sex, age, underlying comorbidity or clinical presentation.

This study demonstrated that predicted strain coverage of the 4CMenB vaccine, against circulating MenB strains in England and Wales, fell between the two observed epidemiological years. This is important to note before the introduction of the vaccine into the national infant immunisation programme, especially in light of a very low estimated coverage among infants in England.

3.3. Study 3

Meningococcal Group W Disease in Infants and Potential Prevention by Vaccination *Emerging Infectious Diseases* (2016)

Sydel R. Parikh, Helen Campbell, Kazim Beebeejaun, Sonia Ribeiro, Steve J. Gray, Ray Borrow, Mary E. Ramsay, Shamez N. Ladhani

3.3.1. Study 3 Aim

This study aimed to assess the historical trends of MenW disease in infants in England in the three most recent epidemiological years (2012-13 to 2014-15) prior to the

introduction of 4CMenB. This was aimed to establish the picture of MenW disease in infants at that time and postulate the number of cases that may be prevented by MenB vaccination, given published evidence (Ladhani et al. 2016) on the potential of 4CMenB to also protect against the hyper-virulent ST-11 MenW strain, which is also prevalent in England and for which no vaccine is licensed for infants

3.3.2. Study 3 Summary

National enhanced surveillance data on laboratory confirmed cases of IMD were used to retrospectively summarise the epidemiology of MenW disease in England across all ages between, the epidemiological years 1998-99 and 2014-15. MenW cases occurring between 2012-13 and 2014-15 in those aged <1 year were looked at by age in months (≤ 11 months). Laboratory data for cases in this group, confirmed by culture, were analyzed phenotypically in order to identify MenW:2a strains, a surrogate phenotypic marker for the hypervirulent ST-11 MenW strain.

3.3.3. Study 3 Results

This study established long term trends of MenW incidence and phenotypic distribution in England over a 17-year period. A total of 176 MenW cases occurred during this time across all age groups where the number of cases peaked during 2000-01 (n=28) due to a national outbreak associated with the Hajj pilgrimage but this soon declined after mandatory vaccination for pilgrims was initiated. MenW cases in infants began to increase again beginning in 2012-13 (n=4), rising to 12 in 2013-14 and in 2014-15 MenW (n=21) accounted for 16.5% of all cases of IMD in infants (n=127). Breakdown of MenW incidence by age in months, before 1 year of age, showed a peak at 4 months of age which remained high until the first birthday.

Phenotypic characterisation can only be performed on cases confirmed by culture and thus it could not be ascertained for cases confirmed by PCR only. Between 2012-13 and 2014-15 a total of 25 (67.5%) of 37 MenW cases in infants were confirmed by culture of which nearly half (n=18; 49%) were characterised as MenW:2a, a surrogate phenotypic marker for the hypervirulent ST-11 MenW strain. Data on age distribution and phenotype suggest that »70% of MenW cases in infants could be prevented by the

introduction of the 4CMenB vaccine at 2 and 4 months of age, while from mid-2016 the booster will be available for children aged 1 year of age and could work to protect toddlers for whom MenW cases were also increasing.

3.3.4. Study 3 New Knowledge gained

This is the first study that established a baseline of the phenotypic epidemiology of MenW cases in infants and it was demonstrated that 4CMenB could protect against circulating MenW:cc11 strains which is important as MenW causes the greatest number of IMD cases in infants in England, after MenB.

Published papers presented in Chapter Two

Study 1: Epidemiology, clinical presentation, risk factors, intensive care admission and outcomes of invasive meningococcal disease in England, 2010-2015. *Vaccine* (2018)

Vaccine 36 (2018) 3876–3881

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Epidemiology, clinical presentation, risk factors, intensive care admission and outcomes of invasive meningococcal disease in England, 2010–2015

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ARTICLE INFO

Article history:
Received 20 October 2017
Received in revised form 2 February 2018
Accepted 6 February 2018
Available online 24 April 2018

Keywords:
Meningococcal disease
Epidemiology
Surveillance
Risk factors
Case fatality

ABSTRACT

The epidemiology of invasive meningococcal disease (IMD) is constantly changing as new strains are introduced into a population and older strains are removed through vaccination, population immunity or natural trends. Consequently, the clinical disease associated with circulating strains may also change over time. In England, IMD incidence has declined from 1.8/100,000 in 2010/2011 to 1.1/100,000 in 2013/2014, with a small increase in 2014/2015 to 1.3/100,000. Between 01 January 2011 and 30 June 2015, MenB was responsible for 73.0% (n = 2489) of 3411 laboratory-confirmed IMD cases, followed by MenW (n = 371, 10.9%), MenY (n = 373, 10.9%) and MenC (n = 129, 3.8%); other capsular groups were rare (n = 49, 1.4%). Detailed questionnaires were completed for all 3411 laboratory-confirmed cases. Clinical presentation varied by capsular group and age. Atypical presentations were uncommon (244/3411; 7.2%), increasing from 1.2% (41/3411) in children to 3.5% (120/3411) in older adults. Known IMD risk factors were rare (18/3411; 0.5%) and included complement deficiency (n = 11), asplenia (n = 6) or both (n = 1). Nearly a third of cases required intensive care (1069/3411; 31.3%), with rates highest in adults. The 28-day CFR was 6.9% (n = 237), with the lowest rates in 0–14 year-olds (85/1885, 4.5%) and highest among 85+ year-olds (30/94, 31.9%). These observations provide a useful baseline for the current burden of IMD in a European country with enhanced national surveillance.

1. Introduction

Invasive meningococcal disease (IMD) is one of the most feared infectious diseases in children and adults due to its sudden onset, rapid progression, serious clinical presentations, high case fatality and long-term sequelae among survivors. The fight against meningococcal disease has advanced with the availability of effective vaccines against the major capsular groups responsible for invasive disease worldwide.

In Europe, group B meningococci (MenB) are responsible for the majority of IMD cases and deaths, especially in children, adolescents and young adults [1]. Group C disease (MenC) is rare, especially in countries with established MenC immunisation programmes. Currently, many countries across Europe are experiencing an increase in IMD due to a highly virulent group W meningococcal strain (MenW) belonging to the ST-11 clonal complex [2].

The UK was first country to offer the MenC conjugate vaccine to all children and adults up to 25 years of age. In August 2015, the UK implemented an emergency immunisation programme offering the quadrivalent meningococcal ACWY conjugate vaccine to teenagers in order to control the rapid increase MenW disease across all age groups [3]. In September 2015, the UK also became the first country to introduce a novel, protein-based vaccine against group B meningococci (MenB) into its nationally-funded, infant immunisation programme [4]. This vaccine has the potential to protect infants against other meningococcal capsular groups, including the hypervirulent ST-11 MenW strain [5]. In anticipation of these two national immunisation programmes, Public Health England enhanced national surveillance to collect more detailed data for cases diagnosed since 2011 in order to complement the laboratory surveillance that was already in place.

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https://doi.org/10.1016/j.vaccine.2018.02.038
0264-410X/

Here we present the epidemiology, capsular group distribution, risk factors, clinical presentation and outcomes of all IMD cases in England over a 5-year period, providing a baseline against which the impact of the two new meningococcal vaccine programmes may be measured in future.

2. Methods

2.1. Surveillance of IMD

Public Health England (PHE) conducts enhanced national IMD surveillance and its Meningococcal Reference Unit (MRU) provides a national reference service for IMD confirmation and characterisation of invasive meningococci (both culture and non-culture). The MRU also provides free non-culture PCR confirmation of meningococcal diagnosis (including genogroup and genosubtype analysis) for clinical specimens that are routinely submitted by National Health Service (NHS) hospitals in England [6], a method that has proven high case ascertainment [7]. In 2013, PHE enhanced the laboratory surveillance by collecting clinical data using postal questionnaires to general practitioners (GPs) of laboratory-confirmed IMD cases diagnosed since 01 January 2011. Information collected included comorbidities, risk factors, clinical presentation, intensive care admission (ICU) and outcomes. Incomplete or missing information in the questionnaires was followed-up by telephoning the GP, contacting the patient's hospital clinician or requesting additional information from the local PHE health protection team (HPT), which maintains records of all suspected and confirmed IMD cases for public health management of cases and close contact and for monitoring outbreaks. If needed, additional information was sought from HPZone, a national web-based case management system used by local Health Protection Teams to record public health events and actions, and from electronic death registration records provided to PHE by the Office for National Statistics for public health surveillance purposes and confirmed dates of death using the Personal Demographics Service (PDS) only including deaths within 28 days of receipt of sample.

2.2. Data

Demographic, clinical questionnaire and microbiological data were entered into a single Microsoft Access Database (Microsoft Corporation, Redmond, Washington) cleaned and de-duplicated before importing into Stata version 13.0 (StataCorp LP, College Station, Texas) for analysis. The final database included all laboratory-confirmed IMD cases in England that were confirmed by the MRU over five epidemiological (July to June) years from 2010/11 to 2014/15. These data were used to calculate national and regional incidence, as well as serogroup distribution of IMD cases. Clinical data are presented for cases diagnosed between January 2011 and July 2015. These data are predominately descriptive and logistic regression analyses were used where appropriate.

3. Results

3.1. IMD incidence

IMD incidence in England declined by 38.9% from 1.8/100,000 (n = 1009) in 2010/11 to 1.1/100,000 (n = 636) in 2013/14, followed by a small increase in 2014/15 at 1.3/100,000 (n = 724) (Fig. 1). The greatest proportional decline was observed in toddlers (10.6/100,000 to 5.8/100,000; 45.3% decrease) and 5–14 year olds (1.8/100,000 to 1.0/100,000; 44.4% decrease), compared to 34.0% in infants (29.1/100,000 to 19.2/100,000). At the same time, IMD incidence increased in older adults, ranging from a 12.5% increase in 65–74 year olds (0.8/100,000 to 0.9/100,000) to 116.7% in 85+ year-olds (1.2/100,000 population to 2.6/100,000 population). Compared to 2013/14, IMD incidence in 2014/15 increased in all age-groups, except infants (21.6/100,000 [n = 151] to 19.2/100,000 [n = 127]) and 25–44 year olds (0.4/100,000 [n = 55] to 0.3/100,000 [n = 48]).

3.2. Capsular group

The incidence of MenB disease nearly halved over the five years, from 1.5/100,000 in 2010/11 (n = 843) to 0.8/100,000 in 2014/15 (n = 418). This decline was observed across all the age-groups and was greatest in toddlers (1–4 years) (10.0/100,000 [n = 278] to 5.0/100,000 [n = 139]; 50% decrease) and infants (27.1/100,000 [n = 195] to 15.2/100,000 [n = 101]; 44% decrease). IMD incidence in 15–24 year-olds also declined by 20% over the same period from 2.0/100,000 (n = 149) to 1.6/100,000 (n = 106).

In contrast, MenW incidence increased from 0.1/100,000 (n = 36; 4% of all IMD cases) in 2010/11 to 0.3/100,000 (n = 176; 24.3% of all IMD cases) in 2014/15. This increase was initially observed in the 15–24 year age group but soon followed across all ages, with the greatest increases seen in infants (0.42 per 100,000 [n = 3] in 2010/11 to 3.01 per 100,000 [n = 21] in 2014/15), such that infants had the highest MenW incidence in 2014/15 compared to any other age group. In 15–24 year olds, MenW incidence increased from 0.08/100,000 (n = 6) in 2010/11 to 0.43/100,000 in 2014/15, when it was responsible for 29.2% (31/106) of all IMD cases in this age group. In older adults, MenW disease was rare but increased rapidly over the five years from 0.04

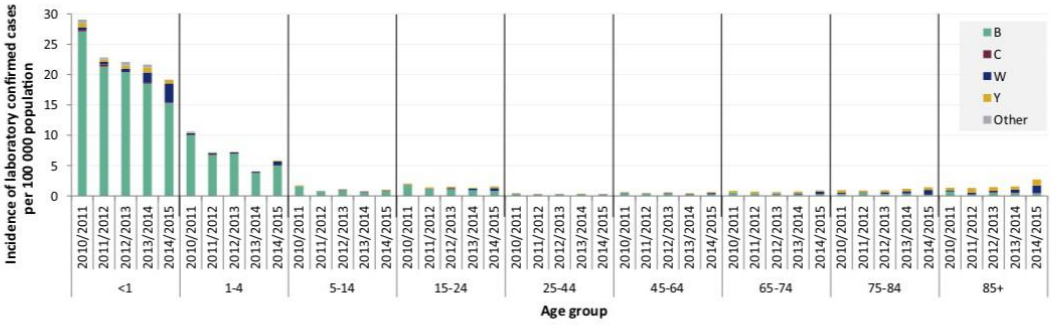

Fig. 1. Incidence by age group stratified by epidemiological year and meningococcal capsular group in England: 2010/11 to 2014/15.

Table 1
Regional distribution of IMD incidence in England during the 2014/15 epidemiological year.

Region	MenB incidence per 100,000 (n)	Men C/W/Y incidence per 100,000 (n)	All IMD incidence per 100,000 (n)
East Midlands	0.73 (34)	0.47 (22)	1.22 (57)
West Midlands	0.92 (53)	0.45 (26)	1.39 (80)
East of England	0.54 (33)	0.36 (22)	0.91 (55)
London	0.54 (47)	0.52 (45)	1.07 (93)
North East	1.33 (35)	0.91 (24)	2.25 (59)
North West	1.24 (89)	0.56 (40)	1.83 (131)
South East	0.55 (49)	0.59 (53)	1.14 (102)
South West	0.62 (34)	0.60 (33)	1.22 (67)
Yorkshire and Humber	0.82 (44)	0.61 (33)	1.48 (80)

per 100,000 (n = 2) to 0.44 per 100,000 (n = 24); a 10-fold increase in 65–74 year-olds, 0.16 per 100,000 (n = 5) to 0.76 per 100,000 (n = 25) in 75–84 year-old and from 0.24 per 100,000 (n = 3) to 1.18 per 100,000 (n = 16) in adults aged 85 years and older. In older adults, the rapid increase in MenW disease offset the decline in MenB disease such that the overall IMD incidence increased across all three older age groups by 2014/15.

IMD incidence due to MenY (0.13–0.17/100,000), MenC (0.04–0.06/100,000) and other capsular groups (0.01–0.04/100,000) remained relatively stable over the five-year period.

3.3. Region

IMD incidence in 2014/15 varied by region (Table 1), from 0.91/100,000 in the East of England (n = 55) to 2.25/100,000 in the North East (n = 59). There were also regional differences in MenB and MenACWY incidence across England. MenB incidence was lowest in London (0.54/100,000; n = 47) and the East of England (0.54/100,000; n = 33) and highest in the North East (1.33/100,000; n = 35). MenA/C/W/Y incidence was lowest in the East of England (0.36 per 100,000; n = 22) and highest in the North East 0.91/100,000 (n = 24).

3.4. Case follow-up

Enhanced national follow-up for IMD was undertaken for all 3411 cases diagnosed in England during 01 January 2011 to 30 June 2015. MenB was responsible for 73.0% (2489/3411) of IMD cases, followed by MenY (373/3411; 10.9%), MenW (371/3411; 10.9%) and MenC (129/3411; 3.8%). More than half the MenB cases (1423/2489; 57.2%) were in children aged <5 years including 25.0% (622/2489) in infants aged <1 year. The contribution of MenB to total IMD cases decreased with age, such that it was only responsible for 24.5% (23/94) of IMD cases in 85+ year-olds compared to 88.4% (622/704) in infants (Table 2).

The 15–24 year age-group had the highest number of MenW cases (69/498; 13.9%) compared to the other age-groups, but this capsular group contributed to a greater proportion of IMD cases in older adults, responsible for over a quarter of cases in those aged 65–74 (47/181, 26.0%), 75–84 years (52/159; 32.7%) and 85+ year-olds (28/94, 29.8%). The distribution of MenY cases was similar to MenW in that cases increased with age, where its contribution to IMD by age group was highest in older adults, ranging from 32.6% (59/181) in 65–74, 33.3% (53/159) in 75–84 to 40.4% (38/94) in 85+ year-olds.

MenC cases were rare, with almost half of all cases diagnosed in 25–64 year-olds (64/129; 49.6%), There were only 37 cases in <15 year olds and 15 in 15–24 year-olds over the five-year surveillance period.

3.5. Clinical presentation

The clinical characteristics of IMD cases in different age-groups are summarised in Table 2. In children under 15 years, over a quarter of cases presented with septicaemia alone (987/3411; 28.9%) and fewer children presented with meningitis only (408/3411; 12.0%) Adolescents and young adults (15–24 years) represented the highest number of cases with meningitis only (220/889 of meningitis cases; 24.7%) and this presentation was responsible for 44.2% of all IMD cases in this age-group (220/498).

In adults, the proportion presenting with meningitis alone and meningitis with septicaemia declined with increasing age, while

Table 2
Characteristics of IMD by age group in England between 01 January 2011 and 30 June 2015.

	<1	1–4	5–14	15–24	25–44	45–64	65–74	75–84	85+	Total
Capsular group	*704*	*870*	*311*	*498*	*244*	*350*	*181*	*159*	*94*	*3411*
B	622 (88.4)	801 (92.1)	254 (81.7)	346 (69.5)	141 (57.8)	185 (52.9)	67 (37.0)	50 (31.4)	23 (24.5)	2489 (73.0)
C	7 (1.0)	8 (0.9)	22 (7.1)	15 (3.0)	36 (14.8)	28 (8.0)	6 (3.3)	2 (1.3)	5 (5.3)	129 (3.8)
W	42 (6.0)	41 (4.7)	10 (3.2)	69 (13.9)	23 (9.4)	59 (16.9)	47 (26.0)	52 (32.7)	28 (29.8)	371 (10.9)
Y	20 (2.8)	10 (1.1)	18 (5.8)	60 (12.1)	41 (16.8)	74 (21.1)	59 (32.6)	53 (33.3)	38 (40.4)	373 (10.9)
Other	13 (1.8)	10 (1.1)	7 (2.3)	8 (1.6)	3 (1.2)	4 (1.1)	2 (1.1)	2 (1.3)	0 (0)	49 (1.4)
Known risk factor	<1	1–4	5–14	15–24	25–44	45–64	65–74	75–84	85+	Total
	0	1 (0.1)	2 (0.6)	5 (1.0)	3 (1.2)	4 (1.1)	3 (1.7)	0	0	18 (0.5)
Clinical presentation	<1	1–4	5–14	15–24	25–44	45–64	65–74	75–84	85+	Total
Meningitis	198 (28.1)	126 (14.5)	84 (27)	220 (44.2)	83 (34)	100 (28.6)	43 (23.8)	23 (14.5)	12 (12.8)	889 (26.1)
Septicaemia	333 (47.3)	513 (59)	141 (45.3)	154 (30.9)	89 (36.5)	131 (37.4)	76 (42)	72 (45.3)	45 (47.9)	1554 (45.6)
Meningitis and Septicaemia	156 (22.2)	214 (24.6)	79 (25.4)	106 (21.3)	58 (23.8)	68 (19.4)	23 (12.7)	12 (7.5)	8 (8.5)	724 (21.2)
Other	17 (2.4)	17 (2)	7 (2.3)	18 (3.6)	14 (5.7)	51 (14.6)	39 (21.5)	52 (32.7)	29 (30.9)	244 (7.2)
Diagnosis confirmation	<1	1–4	5–14	15–24	25–44	45–64	65–74	75–84	85+	Total
PCR only	312 (44.3)	522 (60)	187 (60.1)	259 (52)	105 (43)	121 (34.6)	34 (18.8)	17 (10.7)	3 (3.2)	1560 (45.7)
Culture only	192 (27.3)	116 (13.3)	46 (14.8)	155 (31.1)	97 (39.8)	177 (50.6)	125 (69.1)	137 (86.2)	89 (94.7)	1134 (33.2)
Culture and PCR	200 (28.4)	232 (26.7)	78 (25.1)	84 (16.9)	42 (17.2)	52 (14.9)	22 (12.2)	5 (3.1)	2 (2.1)	717 (21)
ICU admission	<1	1–4	5–14	15–24	25–44	45–64	65–74	75–84	85+	Total
	181 (25.7)	252 (29.0)	102 (32.8)	187 (37.6)	100 (41)	134 (38.3)	75 (41.4)	28 (17.6)	10 (10.6)	1069 (31.3)
28-day Case fatality rate (CFR)	<1	1–4	5–14	15–24	25–44	45–64	65–74	75–84	85+	Total
	28 (4.0)	42 (4.8)	15 (4.8)	31 (6.2)	19 (7.8)	22 (6.3)	23 (12.7)	27 (17)	30 (31.9)	237 (6.9)

the proportion presenting with septicaemia alone increased with age.

Clinical presentations other than meningitis/septicaemia were rare (244/3411; 7.2%) and their prevalence increased with age, from <2.5% in children to 27.6% in older adults. MenY (90/244, 36.9%) and MenW (73/244, 29.9%) were responsible for two-thirds of cases with other clinical presentations. Half the atypical presentations were pneumonia (130/235; 55.3%), with 64.6% (84/130) of pneumonia presentations occurring in older adults (65+ year-olds) and were most common among MenY cases (51/373; 13.7%). Septic arthritis accounted for 36.2% (85/235) of the other presentations, mainly in children aged <5 years (22/85; 25.9%) MenB (14/22; 63.6%) and MenY cases (8/22; 36.4%) were responsible for these presentations in this age group (Table 4). Six percent (14/235) had either epiglottitis or supraglottitis and 2.6% (6/235) presented with skin and soft tissue infection; all these cases except one case of cellulitis were due to MenY (55.0%; 11/20) or MenW (40.0%; 8/20).

3.6. Risk factors

Recorded risk factors for meningococcal disease were rare (0.5% of all IMD, 18/3411); six had asplenia, 11 had complement deficiency and one had both. The responsible capsular groups included MenY (7/18, 38.9%), MenB (6/18, 33.3%), MenW (4/18, 22.2%) and one case of MenC (5.6%). Half the cases presented with meningitis only (50%; 9/18) and three (16.7%) had septicaemia; five (27.8%) required ICU admission and none died.

3.7. Rare capsular groups

Rare capsular groups were responsible for only 1.4% (49/3411) of IMD cases. Nearly half the cases (23/49; 46.9%) were aged <5 years, with cases rarely reported in older adults. Thirty cases (61.2%) were due to an ungroupable capsular group (invasive clinical isolates that were not groupable) and 17 (34.7%) were non-groupable, (culture-negative but PCR screen (ctrA) positive clinical samples which were negative for the four main genogroups [B, C, W and Y] routinely tested for) and one case each of MenA (2.0%) and Men29E (2.0%). The most common presentation was meningitis (21/49; 42.9%), mainly due to ungroupable (19/21; 90.5%) or non-groupable (2/21; 9.5%) isolates. Fifteen cases presented with septicaemia (30.6%), 53.3% were due to non-groupable (8/15) isolates; followed by non-groupable (5/18; 27.8%), group 29E (1/15; 6.7%) and group A (1/15; 6.7%) meningococci. Ten had both presentations (5 nongroupable, 5 ungroupable). Two cases presented with pneumonia (1 non-groupable, 1 ungroupable) and one case of pericarditis was due to a non-groupable strain. The MenA and Men29E cases occurred in adults aged 45–64 years, who presented with septicaemia.

3.8. Diagnostics

Overall, 1.560 cases (45.7%) were diagnosed by PCR only, 1134 (33.2%) by culture only and 717 (21.0%) by both methods. MenW and MenY cases had higher proportions diagnosed by culture only, while MenB was more commonly diagnosed by PCR only (1369/2489; 55.0%). Meningitis was confirmed by PCR only in 59.7% (531/889), compared to 47.1% for meningitis and septicaemia combined (341/724). Other presentations were confirmed mainly by culture only (201/244, 82.4%); bacteraemic pneumonia (115/244; 47.1%) accounted nearly half of these cases.

3.9. Intensive care admissions

Nearly a third of IMD cases required ICU admission (1069/3411; 31.3%). The rate of ICU admissions increased with age to 25–44 years and remained at around 40% up to 65–75 year-olds before declining among older age groups. ICU admission by capsular group was highest for MenC (38.0%; 49/129) and MenW (37.2%; 138/371) followed by MenB (31.1%; 775/2489), MenY (26.8%; 100/373) and other capsular groups (14.3%; 7/49). Those who presented with both meningitis and septicaemia had higher ICU admission rates (45.7% 331/724) compared to those with meningitis only (27.7%; 246/889) and septicaemia only (28.8%; 448/1554). Those with IMD risk factors were just as likely to be admitted to ICU as previously healthy cases [5/18 [27.8%] vs. 1064/3393 [31.4%]; p = 0.93].

3.10. Deaths

Overall, there were 237 deaths across all age-groups categorised as due to IMD, CFR was lower in children ((4.5%; 85/1885) <15 years of age) compared to adults (6.6%; 72/1092 in 15–64 year-olds) and highest in older adults (18.4%; 80/434 in 65 + year-olds). CFR was disproportionately higher in older adults aged 85+ years (Table 2). Children aged <5 years, however, contributed the highest number of deaths (70/237 deaths, 29.5%). Of those who died, over half (56.5%; 134/237) had MenB disease,

Table 3
Characteristics of IMD by clinical outcome in England between 01 January 2011 and 30 June 2015.

Age group	Alive *3174 (93.1)*	Dead *237 (6.9)*	Total *3411*
0	676 (96)	28 (4)	704
1–4	828 (95.2)	42 (4.8)	870
5–14	296 (95.2)	15 (4.8)	311
15–24	467 (93.8)	31 (6.2)	498
25–44	225 (92.2)	19 (7.8)	244
45–64	328 (93.7)	22 (6.3)	350
65–74	158 (87.3)	23 (12.7)	181
75–84	132 (83)	27 (17)	159
85+	64 (68.1)	30 (31.9)	94
Risk Factor	**Alive**	**Dead**	**Total**
Yes	129 (93.5)	9 (6.5)	138
No	3045 (93)	228 (7)	3273
Comorbidity	**Alive**	**Dead**	**Total**
Yes	377 (91.7)	34 (8.3)	411
No	2797 (93.2)	203 (6.8)	3000
Capsular group	**Alive**	**Dead**	**Total**
B	2355 (94.6)	134 (5.4)	2489
C	116 (89.9)	13 (10.1)	129
W	327 (88.1)	44 (11.9)	371
Y	328 (87.9)	45 (12.1)	373
Other	48 (98)	1 (2)	49
Diagnostic sample	**Alive**	**Dead**	**Total**
PCR only	1484 (95.1)	76 (4.9)	1560
Culture only	1013 (89.3)	121 (10.7)	1134
Culture and PCR	677 (94.4)	40 (5.6)	717
Clinical presentation	**Alive**	**Dead**	**Total**
Meningitis	847 (95.3)	42 (4.7)	889
Septicaemia	1415 (91.1)	139 (8.9)	1554
Meningitis and Septicaemia	693 (95.7)	31 (4.3)	724
Other	219 (89.8)	25 (10.2)	244
ICU admission	**Alive**	**Dead**	**Total**
Yes	955 (89.3)	114 (10.7)	1069
No	2219 (94.7)	123 (5.3)	2342

while similar numbers of deaths were due to MenW (18.6%; 44/237) and MenY (19.0%; 45/237), with very few deaths due to MenC (5.5%; 13/237) or other serogroups (0.4%;1/237). MenW cases had a higher CFR overall (11.9%; 44/371) (Table 3), ranging from 2.3% (1/42) in infants to 40.0% (8/20) in those aged 85 and older. CFR was highest in those with other clinical presentations (10.2%; 25/244) followed by septicaemia (8.9%; 139/1554).

4. Discussion

Our follow-up of all laboratory-confirmed IMD cases across a relatively short surveillance period of five years provides detailed insight into the current burden of this rare but aggressive and life-threatening disease in England. The epidemiology of meningococcal disease varies both regionally and over time, as different strains are introduced into the population and others abate naturally or through vaccination [6]. Consequently, the clinical spectrum of IMD will also vary according to the circulating strains at the time.

The epidemiology of IMD in England is similar to that reported in 25 countries across Europe, with an overall annual notification rate of 0.9/100,000 during 2004–14, ranging from 0.3/100,000 in Italy to 2.9/100,000 in Ireland, and an annual decline of 6.6% in all age groups under 50 years [7]. Infants had the highest mean notification rate (16.0/100,000), followed by 1–4 years olds (4.9/100,000), and 15–24 year-olds (1.4/100,000). During 2004–2014, serogroup B accounted for 74% (n = 31,529) and serogroup C for 16% (n = 6573) of cases with known serogroup. Notably, in Europe, overall a relatively high CFR was observed (8.6%), with higher CFR for MenC (14.3%) and MenW (10.2%) compared to MenB (7.4%).

The proportion of cases diagnosed by PCR and culture methods has remained stable in the UK since the early 2000s [10,11] and MenW and MenY had the highest proportion of cases diagnosed by culture, which has been documented elsewhere [12], this difference is most likely due to a greater number of atypical presentations observed with these serogroups.

Our large cohort allowed us to describe clinical presentations, risk factors, severity and outcomes of IMD cases by age and serogroup. It is well documented that individuals with asplenia and complement deficiencies are at increased risk for IMD [13–15] as well as a possible sub-optimal response to vaccination [16,17]. We have reported, for the first time, the low prevalence of known risk factors among IMD cases. This is a reassuring finding and could suggest that the additional measures, including antibiotic prophylaxis, are likely to be protecting these high-risk groups.

The low CFR in all age groups apart from older adults, is notable. The CFR of <5% in children and just over 5% in adults is far lower than previous reports, mainly during the national MenC outbreak, which was associated with more severe disease and higher fatality rates [8]. The lower CFR is likely to be due a number of factors, including less virulent clonal complexes circulating currently, increased awareness of the disease among parents and healthcare professionals, national guidelines specifically targeting IMD, and lower thresholds among healthcare professionals for investigating and treating children with suspected IMD. That a third of children and adults are admitted to ICU would also suggest a more aggressive approach to provide supportive care for suspected cases, which is also likely to have contributed to better outcomes. Consistent with these observations are the low rates of long-term complications among recent survivors of MenB disease, which is also reassuring [9].

The distribution of serogroups by age is well-described, with MenB predominating in children, especially infants, who account for a quarter of all MenB cases annually. Most children were healthy prior to developing IMD and, while most cases developed

Table 4
Characteristics of IMD by serogroup in England between 01 January 2011 and 30 June 2015.

	B		C		W		Y		Other		Total	
Age group	*2489*		*129*		*371*		*373*		*49*		*3411*	
<1	622	(25.0)	7	(5.4)	42	(11.3)	20	(5.4)	13	(26.5)	704	(20.6)
1–4	801	(32.2)	8	(6.2)	41	(11.1)	10	(2.7)	10	(20.4)	870	(25.5)
5–14	254	(10.2)	22	(17.1)	10	(2.7)	18	(4.8)	7	(14.3)	311	(9.1)
15–24	346	(13.9)	15	(11.6)	69	(18.6)	60	(16.1)	8	(16.3)	498	(14.6)
25–44	141	(5.7)	36	(27.9)	23	(6.2)	41	(11.0)	3	(6.1)	244	(7.2)
45–64	185	(7.4)	28	(21.7)	59	(15.9)	74	(19.8)	4	(8.2)	350	(10.3)
65–74	67	(2.7)	6	(4.7)	47	(12.7)	59	(15.8)	2	(4.1)	181	(5.3)
75–84	50	(2.0)	2	(1.6)	52	(14.0)	53	(14.2)	2	(4.1)	159	(4.7)
85+	23	(0.9)	5	(3.9)	28	(7.5)	38	(10.2)	0	0	94	(2.8)
Risk Factor	B		C		W		Y		Other		Total	
Yes	6	(0.2)	1	(0.8)	4	(1.1)	7	(1.9)	0	0	18	(0.5)
No	2483	(99.8)	128	(99.2)	367	(98.9)	366	(98.1)	49	(100)	3393	(99.5)
Clinical presentation	B		C		W		Y		Other		Total	
Meningitis	690	(27.7)	36	(27.9)	60	(16.2)	82	(22.0)	21	(42.9)	889	(26.1)
Septicaemia	1147	(46.1)	57	(44.2)	180	(48.5)	155	(41.6)	15	(30.6)	1554	(45.6)
Meningitis and Septicaemia	585	(23.5)	25	(19.4)	58	(15.6)	46	(12.3)	10	(20.4)	724	(21.2)
Other	67	(2.7)	11	(8.5)	73	(19.7)	90	(24.1)	3	(6.1)	244	(7.2)
Diagnostic method	B		C		W		Y		Other		Total	
PCR only	1369	(55.0)	42	(32.6)	61	(16.4)	58	(15.5)	30	(61.2)	1560	(45.7)
Culture only	556	(22.3)	51	(39.5)	255	(68.7)	257	(68.9)	15	(30.6)	1134	(33.2)
Culture and PCR	564	(22.7)	36	(27.9)	55	(14.8)	58	(15.5)	4	(8.2)	717	(21.0)
ICU admission	B		C		W		Y		Other		Total	
Yes	775	(31.1)	49	(38.0)	138	(37.2)	100	(26.8)	7	(14.3)	1069	(31.3)
No	1714	(68.9)	80	(62.0)	233	(62.8)	273	(73.2)	42	(85.7)	2342	(68.7)
Outcome	B		C		W		Y		Other		Total	
Alive	2355	(94.6)	116	(89.9)	327	(88.1)	328	(87.9)	48	(98.0)	3174	(93.1)
Dead (≤28 days)	134	(5.4)	13	(10.1)	44	(11.9)	45	(12.1)	1	(2.0)	237	(6.9)

septicaemia which is associated with higher morbidity and mortality, nearly all survived the infection.

It is because of this high incidence that, in September 2015, the UK introduced the national infant MenB immunisation programme with the recently-licensed multi-component vaccine, 4CMenB, and early data reporting high vaccine effectiveness and significant reductions in cases of MenB disease among 4CMenB eligible infants are reassuring [4]. Since this vaccine is not serogroup-specific, it should also help protect against other serogroups causing IMD in the vaccine-eligible cohorts [5,10]. MenC disease remains well-controlled because of the successful national immunisation programme with high vaccine coverage; most cases now occur in adults, where they are often associated with travel or immigration [11].

Outside the childhood age group, disease characteristics changed with increasing age, as other serogroups became more prevalent. MenW and MenY are known to cause IMD in older adults, and atypical clinical presentation is not unusual; such as pneumonia, septic arthritis, endocarditis and epiglottitis, as well as supraglottitis [12,13]. The high CFR in older adults, where serogroups W and Y were more prevalent, is likely to be due to underlying comorbidities unrelated to IMD. In the past decade, IMD due to both these serogroups have increased in England [12,13]. Whilst MenY cases increased mainly in older adults and stabilised after a few years, MenW cases increased year on year, because of the introduction of a hypervirulent strain belonging to the ST-11 clonal complex from Latin America; the ST-11 clonal complex was also responsible for the UK MenC outbreak in the 1990s [14]. MenW cases initially increased in 15–24 year old age group but soon spread across all age groups, resulting in the introduction of an emergency teenage MenACWY immunisation programme in August 2015 [3]. After the first year this showed 69% fewer group W meningococcal cases than predicted by trend analysis and no cases in vaccinated teenagers [18].

We have, for the first time, also described IMD epidemiology in England in more detail. Among 65+ year-olds, it is interesting to note that MenY cases became more prevalent with increasing age, as did atypical clinical presentations and diagnosis by culture only. At the same time, while ICU admission rates declined with age, CFR increased rapidly, reaching 32% in 85+ year-olds.

Analysis of IMD incidence by English regions revealed large variations, with higher rates reported in the northern regions, a pattern that was observed more than a decade ago during the peak of the MenC outbreak [15]. Further studies are needed to identify biological and social factors that might help explain these differing rates.

4.1. Strengths and limitations

The strengths of this study lie in the high case ascertainment that we have consistently achieved through provision of a national reference laboratory. We have now supplemented this laboratory-based surveillance with active, prospective follow-up of every single case of laboratory-confirmed IMD in England. Since England has one of the highest rates of IMD in Europe, the large numbers of cases provide a more accurate assessment of disease characteristics due to the different capsular groups (reflecting clonal complex) across the age groups. A limitation, however, is the limited information collected for surveillance purposes, in terms of more detailed clinical (onset, presenting features, progression management, supportive care, complications at discharge), laboratory (white cell count, inflammatory markers, CSF findings) and long-term outcomes. Such information, however, is not readily available using our current data sources, which were mainly developed for public health surveillance purposes. Whilst the CFR associated with IMD continues to fall, there is also a need to determine whether this is associated with changes in long-term neurodevelopmental outcomes among survivors. We are currently collecting detailed clinical information on childhood IMD cases since the introduction of 4CMenB in the national immunisation programme.

5. Conclusions

We have described the current burden of IMD in a high-income European country with established national surveillance, prior to the introduction of two new meningococcal immunisation programmes. The large number of cases allowed us to describe the disease in detail by serogroup and by age group. Our results highlight the changing and dynamic epidemiology of IMD, both between geographical regions and over time. On-going high-quality epidemiological and laboratory-based surveillance will play a critical role in evaluating the impact of the two new meningococcal immunisation programmes in the UK.

References

[1] Control E.C.f.D.P.a. Annual Epidemiological Report 2016 – invasive meningococcal disease; 2014. Available from: <http://ecdc.europa.eu/en/healthtopics/meningococcal/Pages/Annual-epidemiological-report-2016.aspx> [cited 2017 25/05/2017].

[2] Mustapha MM, Marsh JW, Harrison LH. Global epidemiology of capsular group W meningococcal disease (1970–2015): multifocal emergence and persistence of hypervirulent sequence type (ST)-11 clonal complex. Vaccine 2016;34(13):1515–23.

[3] Campbell H. et al. Targeted vaccination of teenagers following continued rapid endemic expansion of a single meningococcal group W clone (sequence type 11 clonal complex), United Kingdom 2015. Eur Surveill 2015;20(28).

[4] Parikh SR et al. Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in England: a national observational cohort study. Lancet 2016;388(10061):2775–82.

[5] Ladhani SN et al. Effectiveness of meningococcal B vaccine against endemic hypervirulent *Neisseria meningitidis* W strain, England. Emerg Infect Dis 2016;22(2):309–11.

[6] Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. Vaccine 2009;27(Suppl 2):B51–63.

[7] Whittaker R et al. The epidemiology of invasive meningococcal disease in EU/EEA countries, 2004–2014. Vaccine 2017;35(16):2034–41.

[8] Campbell H, Ramsay M. A short review of serogroup C meningococcal conjugate vaccines. Eur Infect Dis 2010;5(2):129–34.

[9] Viner RM et al. Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): a case-control study. Lancet Neurol 2012;11(9):774–83.

[10] Parikh SR et al. Meningococcal group W disease in infants and potential prevention by vaccination. Emerg Infect Dis 2016;22(8):1505–7.

[11] Campbell H, Findlow H, Lucidarme J, Andrews N, Linley E, Ladhani S, et al. Serogroup C Neisseria meningitidis disease epidemiology, seroprevalence, vaccine effectiveness and waning immunity in England from 1998/99-2015/16. Eurosurveillance 2017 [submitted for publication].

[12] Ladhani SN et al. Invasive meningococcal capsular group Y disease, England and Wales, 2007–2009. Emerg Infect Dis 2012;18(1):63–70.

[13] Ladhani SN et al. Increase in endemic *Neisseria meningitidis* capsular group W sequence type 11 complex associated with severe invasive disease in England and Wales. Clin Infect Dis 2015;60(4):578–85.

[14] Lucidarme J et al. Genomic resolution of an aggressive, widespread, diverse and expanding meningococcal serogroup B, C and W lineage. J Infect 2015;71(5):544–52.

[15] Shigematsu M et al. National enhanced surveillance of meningococcal disease in England, Wales and Northern Ireland, January 1999-June 2001. Epidemiol Infect 2002;129(3):459–70.

[16] Balmer P et al. Immune response to meningococcal serogroup C conjugate vaccine in asplenic individuals. Infect Immun 2004;72:332–7.

[17] Parikh SR et al. Meningococcal B vaccine failure with a penicillin-resistant strain in a young adult on long-term eculizumab. Pediatrics 2017;140(3).

[18] Campbell H et al. Emergency meningococcal ACWY vaccination program for teenagers to control group W meningococcal disease, England, 2015–2016. Emerg Infect Dis 2017;23(7).

Study 2: Meningococcal serogroup B strain coverage of the multicomponent 4CMenB vaccine with corresponding regional distribution and clinical characteristics in England, Wales and Northern Ireland, 2007-08 and 2014-15: a qualitative and quantitative assessment. Lancet Infectious Diseases (2017)

Meningococcal serogroup B strain coverage of the multicomponent 4CMenB vaccine with corresponding regional distribution and clinical characteristics in England, Wales, and Northern Ireland, 2007–08 and 2014–15: a qualitative and quantitative assessment

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Summary

Background The UK introduced 4CMenB—a multicomponent vaccine against serogroup B meningococcal disease—into the national infant immunisation programme in September, 2015. The Meningococcal Antigen Typing System (MATS) was used to estimate coverage by 4CMenB of invasive meningococcal group B isolates obtained during 2007–08 in England and Wales (MATS coverage). We aimed to repeat the MATS survey for invasive meningococcal group B isolates obtained during 2014–15, before 4CMenB introduction; compare strain coverage between 2007–08 and 2014–15; and investigate associations between MATS coverage, age, region, and disease outcomes.

Methods Invasive serogroup B meningococcal isolates from cases in England, Wales, and Northern Ireland during 2014–15 were assayed using MATS and compared with 2007–08 data. MATS coverage was assessed by geographical region and age group. Clinical characteristics, risk factors, and outcomes were assessed according to MATS coverage for 2014–15 English cases.

Findings In 2014–15, 165 of 251 (66%; 95% CI 52–80) meningococcal group B isolates were estimated by MATS to be covered by 4CMenB, compared with 391 of 535 (73%; 95% CI 57–87) in 2007–08. The proportion of MATS-positive isolates with one vaccine antigen increased from 23% (122 of 535) in 2007–08 to 31% (78 of 251) in 2014–15, whereas the proportion with more than one antigen fell from 50% (269 of 535) to 35% (87 of 251). This effect reflected changes in circulating strains, particularly ST-269 clonal complex strains. MATS coverage increased with age, varied by geographical region, and was associated with more severe disease.

Interpretation In 2014–15, two-thirds of meningococcal group B isolates were predicted to be covered by 4CMenB. Temporal changes in MATS coverage underscore the need for continued monitoring of antigen expression and diversity, particularly in countries with 4CMenB programmes.

Funding Public Health England, GlaxoSmithKline.

Lancet Infect Dis 2017

Published Online
March 30, 2017
http://dx.doi.org/10.1016/S1473-3099(17)30170-6

See Online/Comment
http://dx.doi.org/10.1016/S1473-3099(17)30174-3

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Introduction

In September, 2015, the UK introduced a novel multicomponent vaccine (4CMenB; Bexsero, GlaxoSmithKline Vaccines, Siena, Italy) against serogroup B meningococcal disease into the nationally funded infant immunisation programme.[1] Similar to most European countries, group B is the main serogroup that causes invasive meningococcal disease in the UK, with the highest incidence in infants.[1] Currently licensed glycoconjugate vaccines that target the capsular polysaccharides of serogroups A, C, W, and Y meningococci do not provide any cross-protection against other meningococcal serogroups.[2] The development of polysaccharide-based vaccines against meningococcal group B disease has been hampered because of structural similarities to fetal neural tissue, rendering the polysaccharide poorly immunogenic.[2]

During development of the 4CMenB vaccine, relatively conserved and cross-protective meningococcal group B surface proteins were identified by reverse vaccinology. Three recombinant proteins—factor H binding protein (fHbp) variant 1.1, neisserial heparin-binding antigen (NHBA) peptide 2, and neisserial adhesin A (NadA) variant 3—were included in 4CMenB, along with outer membrane vesicles containing the porin PorA (P1.4) from the New Zealand outbreak strain. Unlike capsular polysaccharides, which tend to be expressed abundantly and are antigenically relatively uniform in invasive meningococci, surface proteins can be sparse and antigenically diverse. Poorly expressed surface proteins and antigenic variability resulting from different mechanisms (eg, mutation or recombination)[3] might result in the binding of insufficient antibodies to promote complement-mediated lysis. Therefore, the ability of 4CMenB to protect against serogroup B meningococcal strains and the breadth of protection depends on the degree of surface expression and the extent to which

Research in context

Evidence before this study

We searched PubMed with the terms "meningococcal B" and any combination of "vaccine", "coverage", "MATS", or "Meningococcal Antigen Typing System". Publication dates and languages were not limited. Initial studies using the Meningococcal Antigen Typing System (MATS) reported the assay to be reliable and reproducible, providing a conservative estimate of 4CMenB coverage. There is an association between the number of vaccine antigens predicted to be covered by MATS and the probability of being killed by immune serum in the serum bactericidal antibody assay. Strains covered by two or more antigens have a 96% probability of being killed compared with at least 80% of strains covered by one antigen. In a large European survey of more than 1000 clinical meningococcal group B isolates from the 2007–08 epidemiological year, MATS predicted that 78% (95% CI 63–90) of all meningococcal group B strains would be killed by post-vaccination sera, with half of all strains and 64% of MATS-positive strains covered by more than one vaccine antigen. Other countries have since reported coverage of meningococcal group B isolates by 4CMenB and, in a global review, coverage as predicted by MATS ranged from 66% in Canada to 91% in the USA. We found one study from Canada reporting regional variation and trends in coverage over time. Our search identified no studies assessing coverage of isolates by 4CMenB associated with clinical disease, severity, or outcome.

Added value of this study

In England, Wales, and Northern Ireland, coverage of meningococcal group B isolates by 4CMenB from patients with invasive meningococcal disease fell between 2007–08 and 2014–15, and coverage by more than one antigen also decreased. These declines were mainly attributable to changes in circulating strains, particularly the ST-269 clonal complex. Regional coverage of isolates as predicted by MATS varied widely and was lower in most regions in 2014–15 compared with 2007–08. By comparison with older children and adults, coverage of meningococcal group B isolates by 4CMenB was lower in infants, who are also less likely to benefit from the cross-protective effects of the vaccine. In England, MATS-positive meningococcal group B strains were more likely to cause invasive meningococcal disease in healthy individuals and more severe disease, in terms of intensive-care admission and death, than were MATS-negative strains.

Implications of all the evidence

Our findings emphasise the complexity of estimating 4CMenB strain coverage and highlight the importance of MATS when assessing vaccine impact on meningococcal group B disease in a population with fluctuating strain coverage. The association we identified between MATS-positive strains and increased severity of disease—although expected—is reassuring because it suggests that immunised infants might develop milder disease. The UK will be the first country to assess the usefulness of MATS for monitoring vaccine impact and to characterise the meningococci causing invasive disease in both vaccinated and unvaccinated cohorts.

vaccine-induced antibodies recognise and bind to these proteins.[4]

The Meningococcal Antigen Typing System (MATS) is a qualitative and quantitative ELISA that quantifies fHbp, NHBA, and NadA expression in combination with the ability of 4CMenB-induced antibodies to recognise these proteins on individual meningococcal isolates.[5] For an isolate to be deemed vaccine-preventable (MATS-positive), either the relative potency of one or more antigens must be greater than the respective positive bactericidal thresholds, which were assigned on the basis of killing using post-vaccination pooled sera from toddlers, or the isolate must possess homologous PorA (P1.4).[4]

The first application of MATS to a large-scale epidemiological survey entailed assaying 1052 sero-group B meningococcal isolates from five European countries obtained during 2007–08; all meningococcal group B isolates possessed at least one gene encoding a major vaccine antigen.[6] MATS predicted that 78% of meningococcal group B isolates from patients across Europe (including 73% in England and Wales) would be killed by post-vaccination serum samples (referred to herein as MATS coverage). Since this survey is now almost a decade old, we aimed to perform a second MATS survey of isolates from patients with invasive serogroup B meningococcal disease in England, Wales, and Northern Ireland during 2014–15, the last epidemiological year before 4CMenB introduction. We then aimed to compare MATS coverage and regional distribution with the corresponding 2007–08 data. We also aimed to assess age distribution, clinical characteristics, and outcomes of invasive meningococcal disease in patients with MATS-positive and MATS-negative meningococcal group B isolates.

Methods

Data collection

Public Health England conducts enhanced national surveillance of invasive meningococcal disease and provides a national reference service for confirmation of this disease and characterisation of invasive meningococci (both culture and non-culture).[7] Confirmed cases in England are followed up routinely with a short questionnaire sent to the patient's family doctor requesting information on comorbidities, clinical presentation, intensive-care admission, and outcomes. We obtained data for all patients in England, Wales, and Northern Ireland diagnosed with invasive serogroup B meningococcal

disease between July 1, 2014, and June 30, 2015. Data for meningococcal group B isolates obtained in 2007–08 have been published previously.[6]

Procedures

We characterised isolates genotypically by multilocus sequence typing[8] and each of the four main 4CMenB antigens. Genotypic characterisation of 2007–08 isolates was done using Sanger sequence analysis.[6] We did genotypic characterisation of 2014–15 isolates using the Illumina platform[7] and with data extracted from the Meningitis Research Foundation's Meningococcus Genome Library, which contains genome sequences for all English, Welsh, and Northern Irish invasive isolates received by the Public Health England Meningococcal Reference Unit since July, 2010, and is populated on an ongoing basis.[9]

We generated MATS data for both epidemiological years (2007–08 and 2014–15) using the same methods described previously.[4,10,11] We determined PorA subtypes by phenotyping,[7] Sanger sequencing, and genome sequencing.[12] We defined predicted strain coverage as the proportion of serogroup B meningococcal isolates with MATS relative potency greater than the positive bactericidal thresholds for one or more antigen or the presence of PorA (P1.4).

For 2007–08 isolates, we calculated log-normal approximation estimates of 95% CIs for all positive bactericidal thresholds and based them on overall assay reproducibility, as described in the MATS laboratory standardisation study.[10] We used new rabbit sera to manufacture fhbp MATS plates for the 2014–15 analysis, but these required reassignment of a new positive bactericidal threshold because they showed a lower affinity for genetically distant and middle-to-low fHbp-expressing strains. We set new specifications using previously described standardisation methods.[10] For 2014–15 isolates, the fHbp positive bactericidal threshold was 0·012 (95% CI 0·008–0·018) compared with 0·021 (0·014–0·031) in 2007–08, whereas NHBA and NadA positive bactericidal thresholds did not change from those set in 2007–08 (0·294 [0·169–0·511] for NHBA; 0·009 [0·004–0·019] for NadA).[13] We stratified the fHbp and NHBA peptides by their relative potencies and plotted them against the positive bactericidal thresholds in MATS. We assigned isolates with relative potency less than the lower limit of quantification (LLOQ) half of the LLOQ (0·0045 for 2007–08 fHbp isolates; 0·002 for 2007–08 NHBA isolates and for both antigens in 2014–15 isolates), and we did not include isolates with peptide frequencies less than 5 (either dataset).

Statistical analysis

We analysed data using Stata SE version 13.1; data are mainly descriptive. We described data that did not follow

For the **Meningitis Research Foundation's Meningococcus Genome Library** see http://www.meningitis.org/genome-library

	2007–08 (n=535)	2014–15 (n=251)
No antigens	144 (27%)	86 (34%)
One antigen	122 (23%)	78 (31%)
fHbp	78 (15%)	63 (25%)
NHBA	42 (8%)	14 (6%)
NadA	0	0
PorA	2 (<1%)	1 (<1%)
Two antigens	184 (34%)	64 (25%)
fHbp + NHBA	160 (30%)	44 (18%)
fHbp + NadA	0	5 (2%)
fHbp + PorA	17 (3%)	12 (5%)
PorA + NHBA	5 (1%)	3 (1%)
NHBA + NadA	2 (<1%)	0
Three antigens	85 (16%)	23 (9%)
fHbp + NHBA + PorA	84 (16%)	23 (9%)
fHbp + NHBA + NadA	1 (<1%)	0

Data are number of isolates (%). fHbp=factor H binding protein. NadA=neisserial adhesin A. NHBA=neisserial heparin-binding antigen. PorA=porin A.

Table 1: **4CMenB antigens affording protection among invasive meningococcal B isolates from England, Wales, and Northern Ireland during 2007–08 and 2014–15**

	2007–08		2014–15	
	MenB isolates (n=535)	MATS coverage (%)	MenB isolates (n=251)	MATS coverage (%)
cc269	176 (33%)	73%	60 (24%)	53%
cc41/44	169 (32%)	94%	82 (33%)	94%
cc213	52 (10%)	17%	26 (10%)	23%
Unassigned	35 (7%)	54%	22 (9%)	64%
cc32	31 (6%)	100%	23 (9%)	93%
cc461	12 (2%)	42%	10 (4%)	10%
cc60	11 (2%)	46%	3 (1%)	67%
cc162	10 (2%)	100%	8 (3%)	88%
cc18	9 (2%)	89%	1 (<1%)	100%
cc35	8 (1%)	38%	9 (4%)	33%
cc11	6 (1%)	100%	0	..
cc282	4 (1%)	50%	0	..
cc22	2 (<1%)	50%	0	..
cc254	2 (<1%)	100%	0	..
cc364	2 (<1%)	0%	1 (<1%)	0
cc8	1 (<1%)	100%	0	..
cc103	1 (<1%)	0%	1 (<1%)	0
cc174	1 (<1%)	0%	0	..
cc226	1 (<1%)	0%	0	..
cc865	1 (<1%)	100%	1 (<1%)	0
cc1157	1 (<1%)	100%	3 (1%)	33%
cc4821	0	..	1 (<1%)	0
Total covered	..	73%	..	66%

Data are number of isolates (%), unless otherwise stated. cc=clonal complex. MATS=Meningococcal Antigen Typing System. MenB=meningococcal serogroup B.

Table 2: **Clonal complex distribution among meningococcal group B isolates from England, Wales, and Northern Ireland in 2007–08 and 2014–15 and MATS coverage within each clonal complex**

	No antigen		fHbp		NHBA		NadA		PorA	
	2007–08	2014–15	2007–08	2014–15	2007–08	2014–15	2007–08	2014–15	2007–08	2014–15
cc103	1 (100%)	1 (100%)	0	0	0	0	0	0	0	0
cc11	0	0	0	0	2 (33%)	0	0	0	0	0
cc1157	0	2 (67%)	1 (100%)	1 (33%)	0	0	0	0	0	0
cc162	0	1 (13%)	3 (30%)	2 (25%)	5 (50%)	3 (38%)	0	0	1 (10%)	0
cc174	1 (100%)	0	0	0	0	0	0	0	0	0
cc18	1 (11%)	0	8 (89%)	1 (100%)	0	0	0	0	0	0
cc213	43 (83%)	18 (75%)	5 (10%)	5 (21%)	3 (6%)	0	0	0	0	1 (4%)
cc22	1 (50%)	0	0	0	0	0	0	0	0	0
cc226	1 (100%)	0	0	0	0	0	0	0	0	0
cc254	0	0	0	0	1 (50%)	0	0	0	0	0
cc269	48 (27%)	26 (45%)	26 (15%)	25 (43%)	13 (7%)	1 (2%)	0	0	0	0
cc282	2 (50%)	0	0	0	0	0	0	0	0	0
cc32	0	3 (13%)	14 (45%)	12 (50%)	0	1 (4%)	0	0	0	0
cc35	4 (50%)	6 (67%)	1 (13%)	0	2 (25%)	3 (33%)	0	0	0	0
cc364	2 (100%)	1 (100%)	0	0	0	0	0	0	0	0
cc41/44	11 (7%)	5 (6%)	5 (3%)	3 (4%)	8 (5%)	6 (7%)	0	0	1 (1%)	1 (1%)
cc461	7 (58%)	9 (90%)	0	1 (10%)	3 (25%)	0	0	0	0	0
cc4821	0	1 (100%)	0	0	0	0	0	0	0	0
cc60	6 (55%)	1 (33%)	2 (18%)	2 (67%)	2 (18%)	0	0	0	0	0
cc8	0	0	0	0	0	0	0	0	0	0
cc865	0	1 (100%)	0	0	1 (100%)	0	0	0	0	0
Unassigned	16 (46%)	8 (38%)	13 (37%)	10 (48%)	2 (6%)	1 (5%)	0	0	0	0

Data are number of isolates (%). Denominators for each clonal complex by year are in table 2. cc=clonal complex. fHbp=factor H binding protein. NadA=neisserial adhesin A. NHBA=neisserial heparin-binding antigen. PorA=porin A.

Table 3: **Numbers of invasive meningococcal group B isolates from England, Wales, and Northern Ireland afforded protection by no or one antigen *vs* clonal complex: 2007–08 and 2014–15**

a normal distribution as median (IQR) and compared them using the Mann-Whitney *U* test. We compared proportions using the χ^2 test or Fisher's exact test, as appropriate. We based 95% CIs for MATS coverage on overall assay reproducibility using a log-normal scale to estimate 95% CIs around the positive bactericidal thresholds for the different antigens, then calculating the proportion of relative potencies falling within the upper and lower limits. We did the same analysis for both epidemiological years (2007–08 and 2014–15). We used logistic regression to assess any association between adverse outcomes (intensive-care admission or death) and MATS positivity (yes or no), after adjusting for age (<1 year, 1–2 years, 3–4 years, or ≥5 years), underlying comorbidity (present or absent), and clinical presentation (meningitis, septicaemia, both, or other).

See Online for appendix

Role of the funding source

Public Health England, which is an executive agency of the UK Department of Health, employs SRP, MER, SNL, LN, SS, JL, SJG, SAC, JF, and RB; GlaxoSmithKline Vaccines employs MS, RDP, MG, LS, and MP. The authors had sole responsibility for study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between July 1, 2014, and June 30, 2015, 764 cases of invasive meningococcal disease were confirmed in England, Wales, and Northern Ireland, including 440 (58%) cases of serogroup B meningococcal disease, of which 251 (57%) were culture-confirmed (appendix pp 7–16). By comparison, in 2007–08, 1289 cases of invasive meningococcal disease were confirmed in England, Wales, and Northern Ireland, with 1123 (87%) serogroup B of which 535 (48%) were confirmed by culture.

In 2014–15, 165 (66%; 95% CI 52–80) of 251 meningococcal group B isolates contained antigens that were covered by 4CMenB, compared with 391 (73%; 57–87) of 535 in 2007–08 (table 1; appendix p 4). For both years, MATS-positivity was most frequently due to coverage by fHbp alone and in combination with NHBA. None of the MATS-positive isolates in either year were covered by all four vaccine antigens. The proportion of isolates covered by more than one vaccine antigen fell from 50% in 2007–08 to 35% in 2014–15, whereas the proportion covered by one antigen increased from 23% to 31%. This difference was mainly attributable to a shift in the

	fHbp + NHBA		fHbp + PorA		fHbp + NadA		NHBA + NadA		NHBA + PorA		fHbp + NHBA + NadA		fHbp + NHBA + PorA	
	2007–08	2014–15	2007–08	2014–15	2007–08	2014–15	2007–08	2014–15	2007–08	2014–15	2007–08	2014–15	2007–08	2014–15
cc103	0	0	0	0	0	0	0	0	0	0	0	0	0	0
cc11	1 (17%)	0	0	0	0	0	2 (33%)	0	0	0	1 (17%)	0	0	0
cc1157	0	0	0	0	0	0	0	0	0	0	0	0	0	0
cc162	0	0	0	0	0	0	0	0	1 (10%)	2 (25%)	0	0	0	0
cc174	0	0	0	0	0	0	0	0	0	0	0	0	0	0
cc18	0	0	0	0	0	0	0	0	0	0	0	0	0	0
cc213	1 (2%)	0	0	0	0	0	0	0	0	0	0	0	0	0
cc22	1 (50%)	0	0	0	0	0	0	0	0	0	0	0	0	0
cc226	0	0	0	0	0	0	0	0	0	0	0	0	0	0
cc254	1 (50%)	0	0	0	0	0	0	0	0	0	0	0	0	0
cc269	85 (48%)	6 (10%)	0	0	0	0	0	0	1 (1%)	0	0	0	3 (2%)	0
cc282	0	0	2 (50%)	0	0	0	0	0	0	0	0	0	0	0
cc32	17 (55%)	4 (17%)	0	0	0	4 (17%)	0	0	0	0	0	0	0	0
cc35	1 (13%)	0	0	0	0	0	0	0	0	0	0	0	0	0
cc364	0	0	0	0	0	0	0	0	0	0	0	0	0	0
cc41/44	46 (27%)	32 (39%)	15 (9%)	11 (13%)	0	0	0	0	3 (2%)	1 (1%)	0	0	80 (47%)	23 (28%)
cc461	2 (17%)	0	0	0	0	0	0	0	0	0	0	0	0	0
cc4821	0	0	0	0	0	0	0	0	0	0	0	0	0	0
cc60	1 (9%)	0	0	0	0	0	0	0	0	0	0	0	0	0
cc8	1 (100%)	0	0	0	0	0	0	0	0	0	0	0	0	0
cc865	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Unassigned	3 (9%)	1 (5%)	0	0	0	1 (5%)	0	0	0	0	0	0	1 (3%)	0

Data are number of isolates (%). Denominators for each clonal complex by year are in table 2. cc=clonal complex. fHbp=factor H binding protein. NadA=neisserial adhesin A. NHBA=neisserial heparin-binding antigen. PorA=porin A.

Table 4: **Numbers of invasive meningococcal group B isolates from England, Wales, and Northern Ireland afforded protection by two or more antigens *vs* clonal complex: 2007–08 and 2014–15**

proportion of isolates covered by both NHBA and fHbp in 2007–08 to a higher frequency of isolates covered by fHbp only in 2014–15.

The clonal complexes cc269, cc41/44, and cc213 accounted for more than two-thirds of meningococcal group B isolates during 2007–08 and 2014–15 (table 2; appendix p 1). The proportion of cc269 isolates decreased by 9%, from 33% in 2007–08 to 24% in 2014–15. MATS coverage of cc269 also decreased, from 73% to 53%, mainly through loss of coverage provided by NHBA, both individually (table 3; appendix p 6) and in combination with fHbp (table 4; appendix p 6). The clonal complex cc41/44 accounted for around a third of isolates and retained very high MATS coverage (94% in both 2007–08 and 2014–15; table 2). MATS coverage for cc213 increased by 6% (from 17% in 2007–08 to 23% in 2014–15) because of a proportional increase in isolates possessing protective fHbp variant 1 (table 3). cc32 representation in isolates increased by more than 3% between 2007–08 and 2014–15, but MATS coverage of this clonal complex declined by 7% (table 2).

The clonal complex cc269 is composed of two major clusters, centred around sequence types (ST)-269 and ST-275, respectively. A large proportion of unassigned isolates share four or more loci with ST-275 on multilocus sequence typing but fewer than four with the founder sequence type ST-269 and, thus, are unassigned to cc269. In 2007–08, this included 15 of 35 unassigned isolates, seven of which were MATS-positive. If these isolates had been included in the ST-275 cluster, the overall number of cc269 isolates would have increased from 176 to 191 (thus, MATS coverage 135 of 191 [71%, rather than 73%; table 2]). In 2014–15, five unassigned isolates could be treated as belonging to the ST-275 cluster, none of which were MATS-positive (thus, MATS coverage 32 of 65 [49%, rather than 53%; table 2]). ST-269 cluster isolates typically have NHBA peptide 21, which is more likely to have a relative potency greater than the positive bactericidal threshold, whereas ST-275 cluster isolates harbour NHBA peptide 17, which is less likely to have a relative potency greater than the positive bactericidal threshold (appendix p 2). Compared with 2007–08, the proportion of isolates with NHBA peptide 21 was lower in 2014–15, whereas those with NHBA peptide 17 remained stable (figure 1; appendix p 2). NHBA peptide 21 coverage decreased by 23% between 2007–08 and 2014–15 (86% [97 of 113] in 2007–08 to 63% [19 of 30] in 2014–15). Similar trends were observed with fHbp peptide subvariants 1·15 and 1·13 (figure 1; appendix p 3), which are associated with the ST-269 and ST-275 clusters, respectively. These

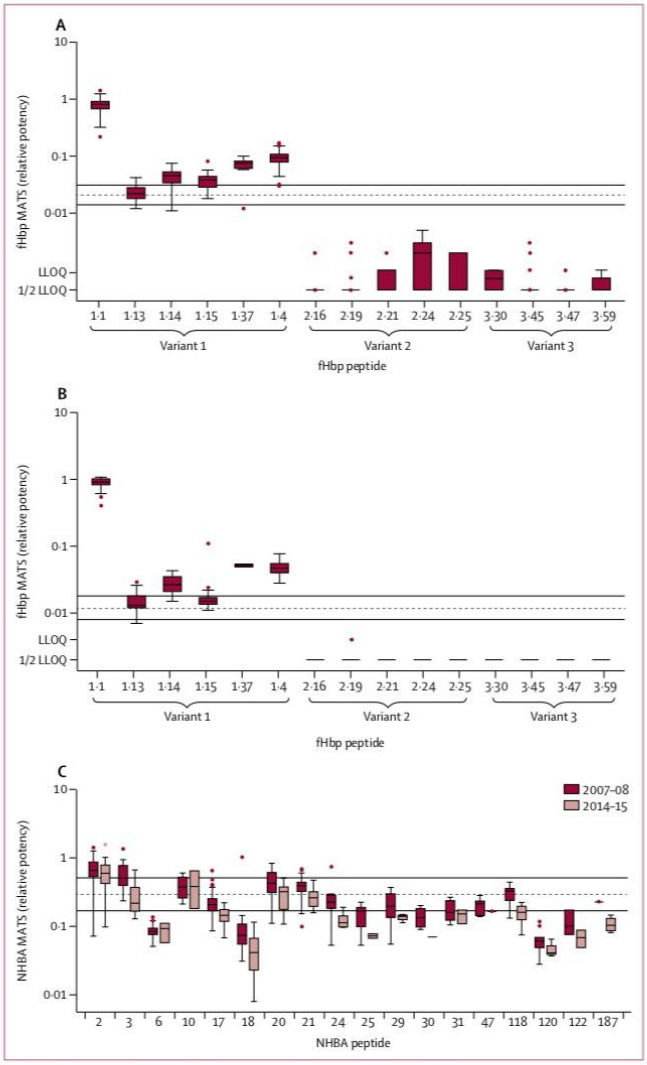

Figure 1: **Distribution of MATS relative potencies of fHbp and NHBA peptides in invasive meningococcal group B isolates in England, Wales, and Northern Ireland during 2007–08 and 2014–15**
(A) fHbp peptide subvariants in 2007–08 (n=442). (B) fHbp peptide subvariants in 2014–15 (n=226). (C) NHBA peptide in 2007–08 and 2014–15 (n=785). Groups accounting for fewer than five isolates are not included in the plots. Boxes represent the median and IQR for each distribution and whiskers signify the 75th percentile + 1·5 × IQR and the 25th percentile – 1·5 × IQR. The horizontal dashed line represents the respective PBT for each antigen and the two horizontal solid lines are the 95% CI. Dots signify individual outliers. LLOQ=0·009 for fHbp in 2007–08, and 0·004 for NHBA in 2007–08 and for both antigens in 2014–15. 1/2 LLOQ=0·0045 for fHbp in 2007–08, and 0·002 for NHBA in 2007–08 and for both antigens in 2014–15. fHbp=factor H binding protein. LLOQ=lower limit of quantification. MATS=Meningococcal Antigen Typing System. NHBA=neisserial heparin-binding antigen. PBT=positive bactericidal threshold.

changes resulted in a decrease in MATS coverage of cc269 in 2014–15.

During 2014–15, 39% of isolates (99 of 251) had one or more proteins homologous to a vaccine antigen compared with 35% (189 of 535) during 2007–08. Coverage by each individual vaccine antigen declined between 2007–08 and 2014–15 (from 64% to 59% for fHbp; from 55% to 33% for NHBA; and from 20% to 16% for PorA), except NadA for which coverage increased (from 1% to 2%; figure 2).

During 2007–08, the fHbp gene was absent in only one (0·19%) of 535 isolates, and two other isolates (0·37%) had frameshift mutations. No deletions or frameshifts were noted among 2014–15 isolates. The overall distribution of fHbp variants remained the same between the two periods, with variant 1 being the most prevalent (70% in 2007–08 and 68% in 2014–15; appendix p 3). MATS coverage of fHbp decreased between 2007–08 and 2014–15, from 63% (333 of 532) to 59% (148 of 251). A 2% increase was recorded in the proportion of isolates with the vaccine-homologous fHbp subvariant 1.1. None of the isolates containing variant 2 or 3 was above the fHbp positive bactericidal threshold for either year (figure 1).

In 2007–08, 18% of meningococcal group B isolates (97 of 535) possessed NadA alleles, including all cc11 (n=6), cc32 (n=31), and cc1157 (n=1) isolates and a proportion of cc213 (47 of 52 [90%]), cc269 (four of 176 [2%]), cc364 (one of two [50%]), cc41/44 (one of 169 [1%]), and unassigned (six of 35 [17%]) isolates. Of the 97 isolates containing NadA alleles, 31 possessed alleles encoding intact peptide subvariants that would potentially be recognised by 4CMenB-induced antibody (NadA-1 and NadA-2/3). However, only three of 535 isolates (1% overall, all cc11) were above the NadA positive bactericidal threshold.

In 2014–15, 22% of meningococcal group B isolates (54 of 251) possessed NadA alleles, including all cc1157 isolates (n=3) and a proportion of cc32 (22 of 23 [96%]), cc213 (23 of 26 [88%]), cc269 (one of 60 [2%]), and unassigned (five of 22 [23%]) isolates. 37% of NadA alleles (20 of 54) encoded intact peptide subvariants that would potentially be recognised by 4CMenB-induced antibody, but only five of 251 isolates (2% overall, four cc32 and one unassigned) were above the NadA positive bactericidal threshold.

The PorA (P1.4) subtype was identified in 20% (107 of 535) and 16% (39 of 251) of isolates in 2007–08 and 2014–15, respectively. This difference was mainly attributable to a lower prevalence of P1.4 among cc41/44 isolates (appendix p 1). Among the remaining isolates, PorA variable region 2 was highly diverse in both periods, with 49 distinct variants belonging to 15 families in 2007–08 and ten families in 2014–15. PorA variable region 2 was deleted in one isolate (belonging to cc41/44) in 2007–08.

The vaccine-homologous NHBA peptide 2 was harboured by a quarter of meningococcal group B isolates for both periods, but MATS-coverage of NHBA

peptide 2 isolates was 3% lower (from 97% in 2007–08 to 94% in 2014–15; figure 1). Three other peptides (21, 17, and 18) accounted for 42% (223 of 535) of the remaining NHBA peptides in 2007–08 and 37% (92 of 251) in 2014–15. The lower MATS coverage of NHBA in 2014–15 was attributable to small reductions across several peptides, most notably, peptide 21.

In 2007–08, 93 (17%) of 535 isolates had fHbp relative potency values less than or equal to the LLOQ compared with 21 (8%) of 251 isolates in 2014–15. Overall, the distribution of fHbp variant 1 was similar between the two periods, with most isolates having relative potencies above the positive bactericidal threshold (figure 1). NHBA peptides, on the other hand, were more variable between the two periods, with a high proportion of isolates falling within or below the 95% CI boundaries (figure 1).

MATS coverage was highest for individuals older than 5 years for both 2007–08 (77%) and 2014–15 (70%). In 2014–15, MATS coverage, and the number of antigens covered, were mostly lower across the age groups, compared with 2007–08 (table 5). In particular, in 2014–15, 37% (26 of 70) of meningococcal group B isolates in infants (age <1 years) were MATS-negative and a further 30% (21 of 70) were only covered by one vaccine antigen (table 5).

MATS coverage varied by UK region; during 2007–08 it was 53–79% and in 2014–15 it was 48–80%. MATS coverage fell in eight of 11 regions, with significant declines in the West Midlands and Yorkshire and Humber (appendix p 4). The increase in MATS coverage in two regions was not significant.

In 2014–15, 231 (92%) of 251 cases were from England. MATS-positivity was associated with a lower prevalence of underlying comorbidities (p=0·002) and, although not significant, intensive-care admissions (p=0·128) and deaths (p=0·874) were higher (appendix p 5). In a logistic regression model, MATS-positivity was associated with a 1·95-fold increased risk (95% CI 1·02–3·76; p=0·017) of severe invasive meningococcal disease (intensive-care admission, death, or both), independent of age, sex, underlying comorbidity, or clinical presentation.

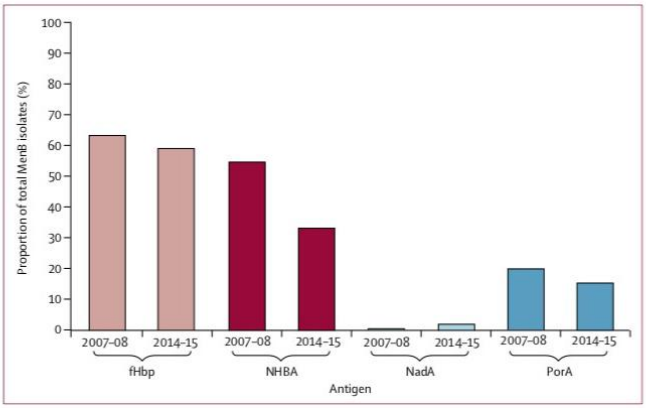

Figure 2: **Proportion of invasive meningococcal group B isolates from England, Wales, and Northern Ireland during 2007–08 and 2014–15 afforded protection by each vaccine antigen**
fHbp=factor H-binding protein. MenB=meningococcal serogroup B. NadA=neisserial adhesin A. NHBA=neisserial heparin-binding antigen. PorA=porin A.

	No antigens	One antigen	Two antigens	Three antigens
2007–08 (n=534*)				
Age <1 years (n=150)	50 (33%)	38 (25%)	45 (30%)	17 (11%)
Age 1–2 years (n=69)	20 (29%)	23 (33%)	14 (20%)	12 (17%)
Age 3–4 years (n=105)	26 (25%)	20 (19%)	40 (38%)	19 (18%)
Age ≥5 years (n=210)	49 (23%)	46 (22%)	80 (38%)	35 (17%)
2014–15 (n=232*)				
Age <1 years (n=70)	26 (37%)	21 (30%)	18 (26%)	5 (7%)
Age 1–2 years (n=55)	21 (38%)	13 (24%)	16 (29%)	5 (9%)
Age 3–4 years (n=15)	7 (47%)	1 (7%)	5 (33%)	2 (13%)
Age ≥5 years (n=92)	28 (30%)	35 (38%)	20 (22%)	9 (10%)

Data are number of isolates (% of age group). MATS=Meningococcal Antigen Typing System. *Age was not reported for one case in 2007–08 and 19 cases in 2014–15.

Table 5: **MATS coverage of invasive meningococcal group B isolates from England, Wales, and Northern Ireland in 2007–08 and 2014–15, stratified by age group**

Discussion

This study provides baseline data for MATS coverage of serogroup B meningococcal disease in England, Wales, and Northern Ireland before introduction of the 4CMenB (Bexsero) vaccine. Cases of serogroup B meningococcal disease more than halved between 2007–08 and 2014–15, from 1123 cases to 440 cases (61% decrease), MATS coverage declined from 73% to 66%, and the proportion of isolates covered by more than one antigen fell from 50% to 35%. In infants younger than 1 year, the age group targeted for vaccination, a third of isolates were MATS-negative and more than a third (37%) were only covered by one vaccine antigen. We found some evidence of more severe disease, in terms of lower comorbidity prevalence and increased risk of intensive-care admissions and death, associated with MATS-positive isolates.

MATS coverage in 2014–15 was lower than in 2007–08, mainly because cases attributable to cc269 (the most prevalent clonal complex in 2007–08) declined, whereas the proportion of the less well covered cc269 sub-population (the ST-275 cluster) increased, resulting in lower coverage attributable to NHBA. This change led to a higher proportion of isolates covered by one antigen (fHbp) only, which potentially could affect the protection offered by 4CMenB. In one study, 80% of strains with one vaccine antigen were killed by immune serum in the serum bactericidal antibody assay compared with 96% for strains with two or more antigens.[4] At the same time, the cross-protection offered by vaccine-induced antibodies is lower in infants compared with children and adults.[4,14–16]

MATS, however, provides a conservative estimate of protection offered by 4CMenB when compared with serum bactericidal antibody assays.[5] For example, some evidence suggests a synergistic effect, whereby antibodies that are not independently bactericidal can augment the killing effect in serum bactericidal antibody assays.[17] Antibodies against minor components of the outer membrane vesicle might also contribute to the killing.[17] Additionally, NadA coverage could be higher than predicted by MATS because NadA expression is repressed under in-vitro growth conditions.[18]

On the other hand, a third of 4CMenB-vaccinated adolescents in a recent US university outbreak had no bactericidal antibodies against the outbreak strain in a human serum bactericidal antibody assay, despite this strain being predicted by MATS to be covered by fHbp and NHBA. However, no additional cases have been reported since the start of the vaccination campaign.[19] In view of the uncertainties surrounding both MATS and serum bactericidal antibody for predicting clinical protection, the early UK data reporting high vaccine effectiveness and significant reductions in cases of serogroup B meningococcal disease among 4CMenB-eligible infants are reassuring.[20]

Previous study findings have shown that the clonal complex does not reliably predict MATS positivity or killing in the serum bactericidal antibody assay because of the dynamic antigenic expression within strains, within clonal complexes, or both.[6,21] The two main cc269 clusters, for example, show different genotypic and phenotypic profiles with respect to the genes encoding 4CMenB antigens and MATS coverage.[22] Furthermore, the diversification of isolates that cluster around ST-275 away from ST-269 underestimates the scale of both the ST-275 cluster and the overall clonal complex, making it difficult to accurately predict coverage of either clonal complex or cluster. Recent genotype-phenotype modeling has shown some promise, with one study estimating 66% coverage for meningococcal group B isolates in the UK and Ireland during 2010–14 using Bexsero Antigen Sequence Type (BAST) scheme.[23]

We assessed MATS coverage by region and found wide variation, even between neighbouring areas, and over time, similar to findings of a Canadian study.[24] This finding is important when interpreting coverage in countries with few cases of serogroup B meningococcal disease, particularly if MATS assessment is undertaken intermittently. MATS-positive strains were also associated with more severe disease, a finding that is, perhaps, not surprising since the selected vaccine antigens are important virulence factors. Immunised infants could, therefore, potentially develop milder disease; this possibility is being monitored after 4CMenB introduction. We did not find any association with clinical presentation, which suggests a more important role for host factors.

The limitations of MATS for predicting killing of specific meningococcal group B strains are well described.[4–6] By using the same laboratory to do MATS testing[6] we could compare regional and national variations in strain coverage over a 7-year interval, although we cannot comment on any trends between these two periods. Since MATS can only be done on cultured isolates, we cannot predict the effect of 4CMenB on culture-negative, PCR-confirmed cases of invasive meningococcal disease, although meningococcal group B isolates are likely to provide good overall genotypic representation of invasive serogroup B meningococcal strains.[25]

In England, a detailed multifaceted plan is in place for enhanced surveillance of invasive meningococcal disease.[26] This surveillance will provide invaluable data for the usefulness of MATS for monitoring vaccine effect and help to characterise the meningococci that cause invasive meningococcal disease in both vaccinated and unvaccinated cohorts.

Contributors

SRP, SNL, and RB did the literature search and wrote the first draft. SRP was responsible for the epidemiological surveillance data. LN, SS, MS, RDP, MG, MM, LS, and MP ran and oversaw all Meningococcal Antigen Typing System assays and collated the outputs for analysis. SRP did the data analysis and prepared the figures. JL prepared genomic data and contributed to their analyses. SRP, JL, JF, SAC, SJG, RB, LS, MER, and SNL contributed to data interpretation. All authors commented on drafts of the report and agreed with the final version.

Declaration of interests

RB, JF, SAC, SS, LN, and SJG perform contract research on behalf of Public Health England for GlaxoSmithKline, Pfizer, and Sanofi Pasteur. JF has also acted on behalf of Public Health England as a consultant and received travel assistance from GlaxoSmithKline and Pfizer. JL reports contract research from GlaxoSmithKline during the conduct of the study. SNL has received research funding on behalf of his institution from GlaxoSmithKline, Pfizer, and Sanofi Pasteur, outside the submitted work. MS, RDP, MG, LS, and MP are employees of GlaxoSmithKline. SRP, MM, and MER declare no competing interests.

Acknowledgments

The study was funded jointly by GlaxoSmithKline Vaccines and Public Health England. We thank all laboratory staff at Public Health England Meningococcal Reference Unit for their assistance with all work related to the Meningococcal Antigen Typing System and the enhanced surveillance of invasive meningococcal disease in the UK; and Kim Taylor, Tracey Smeulders, and Rehana Shivji for facilitating patient follow-up and data entry. For this study, we made use of the Neisseria Multi Locus Sequence Typing website (http://pubmlst.org/neisseria/) developed by Keith Jolley and sited at the University of Oxford; the development of this website has been funded by the Wellcome Trust and European Union. For this study, we also made use of the Meningitis Research Foundation's Meningococcus Genome Library (http://www.meningitis.org/research/genome) developed by Public Health England, the Wellcome Trust Sanger Institute, and the University of Oxford as a collaboration; that project is funded by the Meningitis Research Foundation.

References

1 Ladhani SN, Ramsay M, Borrow R, Riordan A, Watson JM, Pollard AJ. Enter B and W: two new meningococcal vaccine programmes launched. *Arch Dis Child* 2016; **101:** 91–95.
2 Tan LK, Carlone GM, Borrow R. Advances in the development of vaccines against *Neisseria meningitidis*. *N Engl J Med* 2010; **362:** 1511–20.
3 Livorsi DJ, Stenehjem E, Stephens DS. Virulence factors of gram-negative bacteria in sepsis with a focus on *Neisseria meningitidis*. *Contrib Microbiol* 2011; **17:** 31–47.
4 Donnelly J, Medini D, Boccadifuoco G, et al. Qualitative and quantitative assessment of meningococcal antigens to evaluate the potential strain coverage of protein-based vaccines. *Proc Natl Acad Sci USA* 2010; **107:** 19490–95.

5 Frosi G, Biolchi A, Lo Sapio M, et al. Bactericidal antibody against a representative epidemiological meningococcal serogroup B panel confirms that MATS underestimates 4CMenB vaccine strain coverage. *Vaccine* 2013; **31:** 4968–74.

6 Vogel U, Taha M-K, Vazquez JA, et al. Predicted strain coverage of a meningococcal multicomponent vaccine (4CMenB) in Europe: a qualitative and quantitative assessment. *Lancet Infect Dis* 2013; **13:** 416–25.

7 Gray SJ, Trotter CL, Ramsay ME, et al. Epidemiology of meningococcal disease in England and Wales 1993/94 to 2003/04: contribution and experiences of the Meningococcal Reference Unit. *J Med Microbiol* 2006; **55:** 887–96.

8 Jolley KA, Maiden MC. BIGSdb: scalable analysis of bacterial genome variation at the population level. *BMC Bioinformatics* 2010; **11:** 595.

9 Hill DMC, Lucidarme J, Gray SJ, et al. Genomic epidemiology of age-associated meningococcal lineages in national surveillance: an observational cohort study. *Lancet Infect Dis* 2015; **15:** 1420–28.

10 Plikaytis BD, Stella M, Boccadifuoco G, et al. Interlaboratory standardization of the sandwich enzyme-linked immunosorbent assay designed for MATS, a rapid, reproducible method for estimating the strain coverage of investigational vaccines. *Clin Vaccine Immunol* 2012; **19:** 1609–17.

11 Domnich A, Gasparini R, Amicizia D, Boccadifuoco G, Giuliani MM, Panatto D. Meningococcal Antigen Typing System development and application to the evaluation of effectiveness of meningococcal B vaccine and possible use for other purposes. *J Immunol Res* 2015; **2015:** 353461.

12 Jolley KA, Maiden MC. Automated extraction of typing information for bacterial pathogens from whole genome sequence data: *Neisseria meningitidis* as an exemplar. *Euro Surveill* 2013; **18:** 20379.

13 Boccadifuoco G, Stella M, De Paola R, et al. Re-assessment of MATS ELISA specifications. In: Proceedings of the 13th EMGM meeting of the European Meningococcal Disease Society; Amsterdam, Netherlands; Sept 14–17, 2015: pp 60–61 (abstr P37). http://emgm.eu/meetings/emgm2015/EMGM2015_abstracts.pdf (accessed March 3, 2017).

14 Brunelli B, Del Tordello E, Palumbo E, et al. Influence of sequence variability on bactericidal activity sera induced by factor H binding protein variant 1.1. *Vaccine* 2011; **29:** 1072–81.

15 Abad R, Biolchi A, Moschioni M, Giuliani MM, Pizza M, Vazquez JA. A large portion of meningococcal antigen typing system-negative meningococcal strains from Spain is killed by sera from adolescents and infants immunized with 4CMenB. *Clin Vaccine Immunol* 2015; **22:** 357–60.

16 Budroni S, Kleinschmidt A, Boucher P, Medini D. Pooled-sera hSBA titres predict individual seroprotection in infants and toddlers vaccinated with 4CMenB. *Vaccine* 2016; **34:** 2579–84.

17 Giuliani MM, Biolchi A, Serruto D, et al. Measuring antigen-specific bactericidal responses to a multicomponent vaccine against serogroup B meningococcus. *Vaccine* 2010; **28:** 5023–30.

18 Fagnocchi L, Biolchi A, Ferlicca F, et al. Transcriptional regulation of the *nadA* gene in *Neisseria meningitidis* impacts the prediction of coverage of a multicomponent meningococcal serogroup B vaccine. *Infect Immun* 2013; **81:** 560–69.

19 Basta NE, Mahmoud AAF, Wolfson J, et al. Immunogenicity of a meningococcal B vaccine during a university outbreak. *N Engl J Med* 2016; **375:** 220–28.

20 Parikh SR, Andrews NJ, Beebeejaun K, et al. Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in England: a national observational cohort study. *Lancet* 2016; **388:** 2775–82.

21 Abad R, Medina V, Stella M, et al. Predicted strain coverage of a new meningococcal multicomponent vaccine (4CMenB) in Spain: analysis of the differences with other European countries. *PLoS One* 2016; **11:** e0150721.

22 Lucidarme J, Comanducci M, Findlow J, et al. Characterization of fHbp, nhba (gna2132), nadA, porA, sequence type (ST), and genomic presence of IS1301 in group B meningococcal ST269 clonal complex isolates from England and Wales. *J Clin Microbiol* 2009; **47:** 3577–85.

23 Brehony C, Rodrigues CM, Borrow R, et al. Distribution of Bexsero Antigen Sequence Types (BASTs) in invasive meningococcal disease isolates: implications for immunisation. *Vaccine* 2016; **34:** 4690–97.

24 Bettinger JA, Scheifele DW, Halperin SA, et al. Diversity of Canadian meningococcal serogroup B isolates and estimated coverage by an investigational meningococcal serogroup B vaccine (4CMenB). *Vaccine* 2013; **32:** 124–30.

25 Clark SA, Lekshmi A, Lucidarme J, et al. Differences between culture and non-culture confirmed invasive meningococci with a focus on factor H-binding protein distribution. *J Infect* 2016; **73:** 63–70.

26 Public Health England. National enhanced surveillance of vaccination programmes targeting invasive meningococcal disease in England. Dec 10, 2015. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/484661/MeningoEnhancedSurveillancePlan_Final_Dec15.pdf (accessed March 5, 2017).

Study 3: Meningococcal Group W Disease in Infants and Potential Prevention by Vaccination *Emerging Infectious Diseases* (2016)

A675V) require further targeted approaches to relate them to previous reports. In a study in which only PCHL were reported (*5*), the proportion of slowly clearing infections were 69%, 0%, 30%, and 61% for the P441L, E252Q, G538V, and A675V alleles, respectively. Discrepancies can result from confounding pharmacologic (drug level, partner drug), immunologic, and parasitologic (genetic background, parasitic stage at treatment initiation) factors.

RSA results and K13 genotypes were associated with delayed parasite clearance, emphasizing the pertinence of each method to define ART-R. In this area, N458Y is a marker of ART-R. To solve conflicts about specific mutations, more detailed characterization in vitro and in vivo is needed.

Acknowledgments

We thank all the patients and their parents or guardians.

The Shoklo Malaria Research Unit is part of the Mahidol-Oxford University Research Unit, funded by the Wellcome Trust of Great Britain. Laboratory work at Texas Biomedical Research Institute was conducted in facilities constructed with support from Research Facilities Improvement Program grant C06 RR013556 and R017515 from the National Center for Research Resources of the National Institutes of Health and was funded by National Institute of Allergy and Infectious Diseases Grant R37AI048071. This work was supported by grants from the Réseau International des Insituts Pasteur ACIP grant #A14-2012.

M.B., B.W., F.N., and D.M. contributed to the study design. M.B., B.W., and V.D. performed the in vitro assays. T.A., S.N., M.M-W., and K.S. performed the genetic polymorphism analyses. A.P.P. and F.N. coordinated and supervised the clinical studies. M.B., B.W., F.N. and D.M. analyzed the data and wrote the first draft of the manuscript. All authors contributed to the writing of the manuscript.

References

1. Takala-Harrison S, Jacob CG, Arze C, Cummings MP, Silva JC, Dondorp AM, et al. Independent emergence of artemisinin resistance mutations among *Plasmodium falciparum* in Southeast Asia. J Infect Dis. 2015;211:670–9. http://dx.doi.org/10.1093/infdis/jiu491
2. Fairhurst RM. Understanding artemisinin-resistant malaria: what a difference a year makes. Curr Opin Infect Dis. 2015;28:417–25. http://dx.doi.org/10.1097/QCO.0000000000000199
3. World Health Organization. Status report on artemisinin and ACT resistance—September 2015 [cited 2015 Dec 12]. http://www.who.int/malaria/publications/atoz/status-rep-artemisinin-resistance-sept2015.pdf
4. Phyo AP, Nkhoma S, Stepniewska K, Ashley EA, Nair S, McGready R, et al. Emergence of artemisinin-resistant malaria on the western border of Thailand: a longitudinal study. Lancet. 2012; 379:1960–6. http://dx.doi.org/10.1016/S0140-6736(12)60484-X
5. Ashley EA, Dhorda M, Fairhurst RM, Amaratunga C, Lim P, Suon S, et al. Spread of artemisinin resistance in *Plasmodium falciparum* malaria. N Engl J Med. 2014;371:411–23. http://dx.doi.org/10.1056/NEJMoa1314981
6. White LJ, Flegg JA, Phyo AP, Wiladpai-ngern JH, Bethell D, Plowe C, et al. Defining the *in vivo* phenotype of artemisinin-resistant falciparum malaria: a modelling approach. PLoS Med. 2015;12. http://dx.doi.org/10.1371/journal.pmed.1001823
7. Witkowski B, Amaratunga C, Khim N, Sreng S, Chim P, Kim S, et al. Novel phenotypic assays for the detection of artemisinin-resistant *Plasmodium falciparum* malaria in Cambodia: in-vitro and ex-vivo drug-response studies. Lancet Infect Dis. 2013;13:1043–9. http://dx.doi.org/10.1016/S1473-3099(13)70252-4
8. Ariey F, Witkowski B, Amaratunga C, Beghain J, Langlois AC, Khim N, et al. A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria. Nature. 2013;505:50–5. http://dx.doi.org/10.1038/nature12876
9. Straimer J, Gnadig NF, Witkowski B, Amaratunga C, Duru V, Ramadani AP, et al. Drug resistance. K13-propeller mutations confer artemisinin resistance in *Plasmodium falciparum* clinical isolates. Science. 2015;347:428–31. http://dx.doi.org/10.1126/science.1260867
10. Wang Z, Wang Y, Cabrera M, Zhang Y, Gupta B, Wu Y, et al. Artemisinin resistance at the China-Myanmar border and association with mutations in the K13 propeller gene. Antimicrob Agents Chemother. 2015;6952–9. http://dx.doi.org/10.1128/AAC.01255-15

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Meningococcal Group W Disease in Infants and Potential Prevention by Vaccination

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DOI: http://dx.doi.org/10.3201/eid2208.160128

To the Editor: We recently reported that postvaccination serum samples from infants immunized with a novel, protein-based multicomponent meningococcal serogroup B (MenB) vaccine (Bexsero; GlaxoSmithKline Vaccines, Verona, Italy) have bactericidal activity against the hypervirulent meningococcal group W (MenW) strain belonging to the sequence type (ST) 11 clonal complex (*1*). Historically, MenW has been a rare cause of invasive meningococcal disease (IMD), accounting for <5% of confirmed cases in England and Wales (*2*). Since 2009, MenW cases caused by

this hypervirulent strain have rapidly increased in England (*2*). During the 2014–15 epidemiologic year (July 1–June 30), this capsular group accounted for 176 (24%) of 724 IMD cases in England (*3*). In response to this outbreak, in August 2015, the United Kingdom introduced an emergency adolescent conjugate vaccination program against meningococcal capsular groups ACW and Y. Over 2 years, the program aims to provide vaccine to all youth 13–18 years of age and to new university entrants <25 years of age. This program is expected to protect adolescents (25 of 176 [14%] MenW cases during 2014–15 were in those 15–19 years of age), and, by targeting youth with the highest carriage rates, to protect others through indirect (herd) protection, which has been consistently observed in vaccine programs, including that for meningococcal group C (*4,5*). Indirect protection associated with the adolescent immunization program will likely take several years to manifest (*6*).

Infants <1 year of age have the highest incidence of IMD and the highest number of IMD cases and deaths (*5*). During the 2014–15, 127 (18%) of the 724 IMD cases in England occurred in this group: 101 (80%) meningococcal group B (MenB) cases, 21 (16%) MenW cases, 1 (1%) group C case, and 4 (3%) group Y cases (*7*). In September 2015, MenB vaccine was introduced into the UK infant immunization program under a 2-, 4-, and 12-month schedule. We analyzed the epidemiology and long-term trends for MenW disease in infants in England to assess the potential effects of the infant MenB immunization program for preventing MenW cases in this highly vulnerable age group.

During the epidemiologic period 1998–99 through 2014–15, a total of 176 MenW cases were confirmed in infants. The number of cases peaked during 2000–01 (n = 28) because of a national outbreak associated with the Hajj pilgrimage and then declined rapidly after mandatory vaccination for pilgrims was instigated (Figure, panel A). During that outbreak, most infants acquired the infection indirectly from family members who traveled to the Hajj, highlighting this group's susceptibility to IMD. The number of MenW cases in infants began increasing again from 4 cases in 2012–13 to 12 in 2013–14 and 21 in 2014–15. During 2014–15, these 21 MenW cases represented 16.5% of 127 total IMD cases among infants, 12% of 176 total MenW cases, and 3% of 724 total IMD cases in England. All infants with MenW IMD resided in England and had not traveled abroad. The number of MenW cases increased from birth among infants, peaking at 4 months of age and remaining high until the first birthday. Most (123 [70%]) of the 176 MenW cases confirmed during (44/66 [67%]) and after (79/110 [72%]) the Hajj outbreak were in persons ≥5

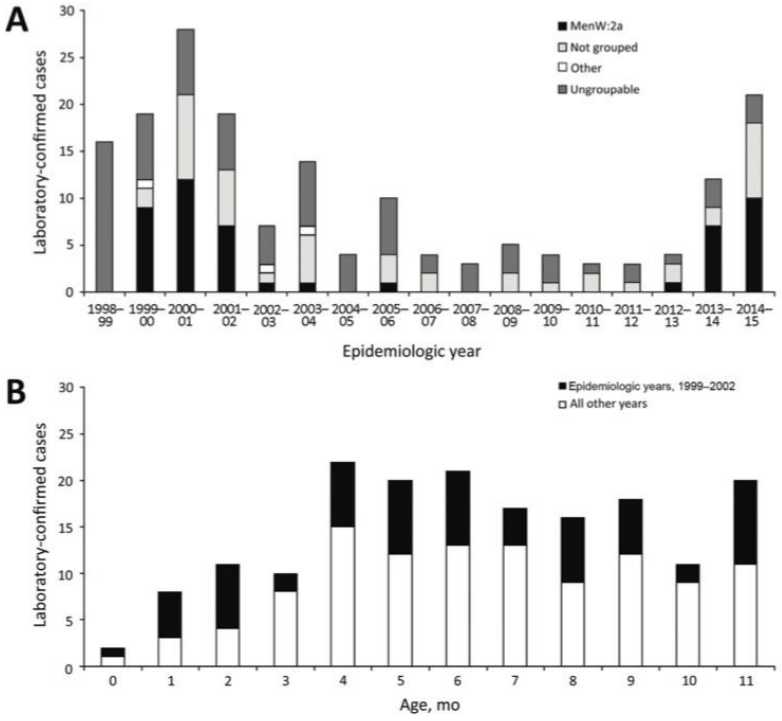

Figure. Incidence of invasive meningococcal disease (IMD) in infants <1 year of age in England during the epidemiologic years 1998–99 through 2014–15. A) Incidence of IMD and phenotypic characterization of laboratory-confirmed meningococcal group W strains in infants <1 year of age. B) Total laboratory-confirmed meningococcal group W cases in infants <1 year of age by month of age. Cases related to the Hajj outbreak occurred during 1999–00 through 2001–02.

months of age and were potentially preventable by MenB vaccine vaccination.

During 2012–13 through 2014–15, a total of 25 (67.5%) of 37 MenW cases in infants were confirmed by culture; 18 (49%) of these cases were phenotypically characterized as MenW:2a, a surrogate phenotypic marker for the hypervirulent ST11 MenW strain. Ten (48%) of the 21 isolates from infants during 2014–15 were MenW:2a, compared with 1 (25%) of 4 during 2012–13 (Figure, panel B). Final diagnoses reported for 20 infants included meningitis (n = 10 [50%]), septicemia (n = 3 [15%]), both meningitis and septicemia (n = 5 [10%]), and septic arthritis (n = 1 [2%]). From 1998–99 through 2014–15, six infants died of MenW IMD (case-fatality rate 3.4%). Four of those deaths occurred during the Hajj outbreak; only 1 death attributed to MenW occurred during the 3 most recent epidemiologic years.

The rapid increase in MenW cases among infants, particularly most recently (2014–15), is cause for concern, and the contemporaneous introduction of MenB vaccine into the national immunization schedule is timely. Although this vaccine is licensed for prevention of MenB disease, the antigens are not specific to this capsular group and could protect against other meningococcal capsular groups that share the same antigens as those in the vaccine. Infants and toddlers immunized with MenB vaccine are expected to develop bactericidal antibodies against ST11 MenW. Data on age distribution suggest that ≈70% of MenW cases in infants could be prevented by MenB vaccination at 2 and 4 months of age. Beginning in mid-2016, the MenB vaccine booster for children 1 year of age is also expected to protect toddlers, for whom MenW cases have also rapidly increased (*3*).

Acknowledgments

We appreciate and acknowledge the hard work of the surveillance team at Public Health England Colindale, the laboratory staff at Public Health England's Meningococcal Reference Unit, and local health protection teams.

References

1. Ladhani SN, Giuliani MM, Biolchi A, Pizza M, Beebeejaun K, Lucidarme J, et al. Effectiveness of meningococcal B vaccine against endemic hypervirulent *Neisseria meningitidis* W strain, England. Emerg Infect Dis. 2016;22:309–11. http://dx.doi.org/10.3201/eid2202.150369
2. Ladhani SN, Beebeejaun K, Lucidarme J, Campbell H, Gray S, Kaczmarski E, et al. Increase in endemic *Neisseria meningitidis* capsular group W sequence type 11 complex associated with severe invasive disease in England and Wales. Clin Infect Dis. 2015;60:578–85. http://dx.doi.org/10.1093/cid/ciu881
3. Campbell H, Saliba V, Borrow R, Ramsay M, Ladhani SN. Targeted vaccination of teenagers following continued rapid endemic expansion of a single meningococcal group W clone (sequence type 11 clonal complex), United Kingdom 2015. Euro Surveill. 2015;20:21188. http://dx.doi.org/10.2807/1560-7917.ES2015.20.28.21188
4. Ramsay ME, Andrews NJ, Trotter CL, Kaczmarski EB, Miller E. Herd immunity from meningococcal serogroup C conjugate vaccination in England: database analysis. BMJ. 2003;326:365–6. http://dx.doi.org/10.1136/bmj.326.7385.365
5. Trotter CL, McVernon J, Ramsay ME, Whitney CG, Mulholland EK, Goldblatt D, et al.; SAGE subgroup. Optimising the use of conjugate vaccines to prevent disease caused by *Haemophilus influenzae* type b, *Neisseria meningitidis* and *Streptococcus pneumoniae*. Vaccine. 2008;26:4434–45. http://dx.doi.org/10.1016/j.vaccine.2008.05.073
6. Ladhani SN, Christensen H, Trotter C, Ramsay ME. Indirect impact of an adolescent meningococcal ACWY conjugate vaccine programme in England with and without catch-up: a transmission dynamic model. Presented at: 13th Congress EMGM, European Meningococcal Disease Society; 2015 September 14–17; Amsterdam, the Netherlands. Abstract 5.01. http://emgm.eu/meetings/emgm2015/EMGM2015_programme.pdf
7. Public Health England. Infection report. Invasive meningococcal disease (laboratory reports in England): 2014/2015 annual data by epidemiological year. Health Protection Report. 2015;9(38) [cited 2016 Mar 23]. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/498057/hpr3815_imd-crrctd.pdf

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Novel Reassortant Avian Influenza A(H5N6) Viruses in Humans, Guangdong, China, 2015

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DOI: http://dx.doi.org/10.3201/eid2208.160146

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Chapter Three

2. Impact and effectiveness of the 4CMenB vaccine in the national infant immunisation programme in England

3.1. Study 4

Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in England: a national observational cohort study *The Lancet* (2016)

Sydel R Parikh, Nick J Andrews, Kazim Beebeejaun, Helen Campbell, Sonia Ribeiro, Charlotte Ward, Joanne M White, Ray Borrow, Mary E Ramsay, Shamez N Ladhani

3.1.1. Study 4 Aim

This study aimed to generate data on early estimates of the impact of the 4CMenB vaccine against MenB disease in infants and also the vaccine effectiveness (VE) against MenB disease in immunized individuals in England after the first 10 months of investigation of the vaccine into the national programme.

3.1.2. Study 4 Summary

Data from the enhanced national surveillance of IMD was used to ascertain the number of confirmed MenB cases in vaccine eligible infants. This was followed up with local PHE health protection teams, general practitioners and hospital clinicians to collect demographic data, vaccination history, clinical presentation and determine the outcomes of disease. For cases diagnosed between 01 September, 2015 and 30 June, 2016, vaccine effectiveness was assessed using the screening method (Farrington, 1993). VE was calculated for at least one dose and two doses based on specific ages including a comparator group (Table 3) and allowing for 2 weeks (14 days) for the development of an adequate immune response. Population vaccine coverage in England was obtained from ImmForm, an online system used by PHE to collect vaccine

coverage data for some national immunisation programmes. Since ImmForm does not collect individual dates of birth or vaccination, vaccine coverage for comparators was estimated by adjusting the 6-month ImmForm coverage using actual dates of birth and dates of vaccination for about 36,000 infants receiving their first dose and about 26,000 receiving their second dose as supplied by five Child Health Information Systems (CHIS). This was performed in order to control for any confounding by age and time, for each MenB case.

Table 3: Definitions of the ages used by vaccine effectiveness dose

VE assessed	Definition of age used
At least one dose	77 days (11 weeks of age)
Two doses	133 days (17 weeks of age)
Comparator group	For each MenB case: all infants in England who were born in the same month at an age in days exactly 14 days younger than the age of the case on the specimen date

Vaccine impact was estimated for vaccine-eligible MenB cases (born on or after 01 May 2015 aged 10 weeks or older and diagnosed between 01 September 2015 and 30 June 2016). Incidence rate ratios (IRRs) were estimated for vaccine eligible cases compared to cases diagnosed in the equivalent time period during the 4 years before vaccine introduction.

3.1.3. Study 4 Results

This study provided the first evidence of protection against group B meningococcal disease conferred by the novel multicomponent 4CMenB vaccine in infants. In England, vaccine coverage was shown to be high in all eligible cohorts, reaching 95.5% for one dose and 88.6% for two doses. During the study period, 37 cases of MenB occurred in

vaccine eligible infants (born on or after 01 May 2015 aged ≥ 10 weeks at diagnosis) and vaccination history was obtained for all cases. Two dose vaccine effectiveness of 82.9% (CI 24.1-95.2) against all MenB disease was equivalent to 94.2% against the highest predicted MenB strain coverage estimate of 88% (Frosi et al., 2013). Compared to the period prior to vaccine introduction, there was a 50% IRR reduction in MenB cases in the vaccine eligible cohort (37 cases vs 74 cases; IRR 0.50 [CI 0.36-0.71]; p=0.0001) which was irrespective of the infants' vaccination status or predicted strain coverage. A non-significant 14% reduction was also observed in the unvaccinated cohort. However, when adjusting for this 14% disease reduction in the unvaccinated cohort, it was estimated that there was a 42% reduction (relative IRR 0.58 [CI 0.40-0.85]; p=0.005) in the vaccine eligible cohort.

3.1.4. Study 4 New knowledge gained

This study provided the first evidence of protection against MenB disease as conferred by the 4CMenB vaccine in infants. These results showed a significant reduction in cases of MenB among vaccine-eligible infants within 10 months of the vaccine's introduction in England. This study also showed that although the vaccine was licensed using a three-dose priming schedule in infancy, short-term VE against MenB disease was high even after two doses.

3.2. Study 5

Vaccination of Infants with Meningococcal Group B Vaccine (4CMenB) in England
***The New England Journal of Medicine* (2020)**
Shamez N Ladhani, Nick Andrews, Sydel R Parikh, Helen Campbell, Joanne White, Michael Edelstein, Xillian Bai, Jay Lucidarme, Ray Borrow, Mary E Ramsay

3.2.1. Study 5 Aim

This study used data from the enhanced national surveillance of IMD to evaluate the effect and effectiveness of 4CMenB in relation to invasive meningococcal group B disease in infants and children at 1 year of age and 2 years of age after the first 3 years of the national immunisation program in England.

3.2.2. Study 5 Summary

The methods in this study were carried out as described in Study 4 using data on vaccine coverage in England routinely collected through primary care and child health information systems. The following adaptations were made: In addition to reporting the percentage of eligible children who received two doses by 12 months and three doses by 18 months the timing of vaccination in days of age was calculated with the use of individual level data from local CHIS. The population effect was estimated with the use of national surveillance data on cases of laboratory confirmed MenB disease. Change in disease incidence was calculated from 4 pre-vaccine surveillance years (September through the following August) to the first 3 complete years after 4CMenB was introduced. The age groups used and their dose eligibilities during the study period were summarised (Table 4).

Table 4: Summary of 4CMenB eligibility by epidemiological year as assessed in VE calculations

	Epidemiological year		
Age	2015-16	2016-17	2017-18
0-8 weeks	Too young to be vaccinated		
9-17 weeks			
18-51 weeks			
1 year			
2 years			
3-4 years	Too old to have been vaccinated during the study period		

Part of group eligible for 1 dose	Entire group eligible for 1 dose
Part of group eligible for 2 doses	Entire group eligible for 2 doses
Part of group eligible for 3 doses	Entire group eligible for 3 doses
Not eligible	

Since the 4CMenB vaccine did not protect against all meningococcal group B strains, the results of the MATS testing of isolates of invasive MenB cases obtained from vaccinated children were used to estimate the vaccine strain coverage of meningococci causing invasive disease in the different vaccinated cohorts. To estimate the vaccine effectiveness against vaccine-preventable meningococcal group B strains only, the vaccine effectiveness against all MenB (vaccine effectiveness $_{all}$) was adjusted by applying the proportion (p) of culture-confirmed cases in vaccinated children that were MATS-positive to the total number of confirmed cases of MenB disease with MATS results in that cohort.

3.2.3. Study 5 Results

This study provided the first estimates of vaccine effect and effectiveness for a complete 2+1 schedule of 4CMenB using data from the first three years of the national immunisation programme. It also showed the sustained impact of the 4CMenB against MenB disease in infants. It was demonstrated that vaccine coverage remained high and data from 3 months of 2018 showed that 92.5% of children had completed the primary immunisations by their first birthday and 87.9% had received all three doses by 2 years. From 01 September 2015 to 31 August 2018, the incidence of MenB disease in England was significantly lower in vaccine-eligible cohorts than the expected incidence (63 observed cases as compared with 253 expected cases; IRR, 0.25; [CI 0.19-0.36]) with a 75% reduction in age groups that were fully eligible for vaccination.

The adjusted VE against MenB disease was 52.7% (95% CI, −33.5 to 83.2) with a two-dose priming schedule for infants and 59.1% (95% CI, −31.1 to 87.2) with a two-dose priming schedule plus a booster at 1 year). Although these VE dropped significantly from the early estimates after the first 10 months of the programme, during this 3-year study period, there were 169 cases of MenB disease in the vaccine- eligible cohorts, with an estimated 277 cases (95% CI, 236 to 323) prevented.

3.2.4. Study 5 New knowledge gained

This study provided evidence that the 4CMenB program was associated with a continued positive effect against MenB disease in children in England. Further, the vaccine regime showed protection after three doses of the vaccine and this protection was sustained for at least 2 years. This evidence provided further support in favour of the effectiveness of a reduced 4CMenB vaccination schedule. This work provides information that will help other European countries since it provides evidence in favour of introducing their own MenB vaccination programmes.

Published papers presented in Chapter Three

Study 4: Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in England: a national observational cohort study *The Lancet* (2016)

Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in England: a national observational cohort study

Sydel R Parikh, Nick J Andrews, Kazim Beebeejaun, Helen Campbell, Sonia Ribeiro, Charlotte Ward, Joanne M White, Ray Borrow, Mary E Ramsay, Shamez N Ladhani

Summary

Background In September, 2015, the UK became the first country to introduce the multicomponent group B meningococcal (MenB) vaccine (4CMenB, Bexsero) into a publicly funded national immunisation programme. A reduced two-dose priming schedule was offered to infants at 2 months and 4 months, alongside an opportunistic catch-up for 3 month and 4 month olds. 4CMenB was predicted to protect against 73–88% of MenB strains. We aimed to assess the effectiveness and impact of 4CMenB in vaccine-eligible infants in England.

Methods Public Health England (PHE) undertakes enhanced surveillance of meningococcal disease through a combination of clinical, public health, and laboratory reporting. Laboratory-confirmed cases of meningococcal disease are followed up with PHE local health protection teams, general practitioners, and hospital clinicians to collect demographic data, vaccination history, clinical presentation, and outcome. For cases diagnosed between Sept 1, 2015, and June 30, 2016, vaccine effectiveness was assessed using the screening method. Impact was assessed by comparing numbers of cases of MenB in vaccine-eligible children to equivalent cohorts in the previous 4 years and to cases in vaccine-ineligible children.

Findings Coverage of 4CMenB in infants eligible for routine vaccination was high, achieving 95·5% for one dose and 88·6% for two doses by 6 months of age. Two-dose vaccine effectiveness was 82·9% (95% CI 24·1–95·2) against all MenB cases, equivalent to a vaccine effectiveness of 94·2% against the highest predicted MenB strain coverage of 88%. Compared with the prevaccine period, there was a 50% incidence rate ratio (IRR) reduction in MenB cases in the vaccine-eligible cohort (37 cases *vs* average 74 cases; IRR 0·50 [95% CI 0·36–0·71]; p=0·0001), irrespective of the infants' vaccination status or predicted MenB strain coverage. Similar reductions were observed even after adjustment for disease trends in vaccine-eligible and vaccine-ineligible children.

Interpretation The two-dose 4CMenB priming schedule was highly effective in preventing MenB disease in infants. Cases in vaccine-eligible infants halved in the first 10 months of the programme. While ongoing national surveillance will continue to monitor the longer-term impact of the programme, these findings represent a step forward in the battle against meningococcal disease and will help reassure that the vaccine protects against this deadly infection.

Funding Public Health England.

Published Online
October 27, 2016
http://dx.doi.org/10.1016/
S0140-6736(16)31921-3

See Online/Comment
http://dx.doi.org/10.1016/
S0140-6736(16)32061-X

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Introduction

In September, 2015, the UK became the first country to introduce the multicomponent, protein-based meningococcal vaccine (4CMenB; Bexsero, GSK, Rixensart, Belgium) into a national, publicly funded infant immunisation programme.[1] The vaccine was offered to all infants born since July 1, 2015, at 2 months, 4 months, and 12 months alongside their routine immunisations. Catch-up vaccination was also opportunistically offered to 3 month and 4 month olds attending their routine immunisation visits, who were eligible for a 3-4-12 month and 4-12 month schedule, respectively.

Before introduction of 4CMenB, the UK immunisation schedule had included the group C meningococcal (MenC) conjugate vaccine since 1999.[2] As an emergency response to a national outbreak of group W meningococcal (MenW) disease, 13–18 year olds and new university entrants have been offered the quadrivalent MenACWY conjugate vaccine since August, 2015.[3] These conjugate vaccines target the polysaccharide capsule of meningococci and do not offer cross-protection against other meningococcal capsular groups, such as group B (MenB), which remains responsible for most cases of invasive meningococcal disease in the UK, especially in young children.[1]

Development of an effective conjugate vaccine against MenB has not been possible because its polysaccharide capsule is structurally homologous to glycoproteins in fetal neural cell adhesion molecules, making them poorly immunogenic self-antigens.[4] 4CMenB is a novel vaccine composed of three recombinant proteins—factor H-binding protein (fHbp), Neisserial heparin-binding antigen (NHBA), and Neisserial adhesin A (NadA)—and the outer membrane vesicles (OMV) from the New Zealand outbreak strain (NZ98/254), which incorporates the immunodominant Porin A (PorA) P1.4 protein.[5] The vaccine was licensed in Europe in January, 2013, on the

Research in context

Evidence before this study

We searched PubMed with the terms "4CMenB", "Bexsero", "meningococcal serogroup B vaccine", and any combination of "vaccine effectiveness" or "impact". Publication dates and languages were not limited. Our search results identified no data for the vaccine effectiveness or impact of 4CMenB against invasive meningococcal group B (MenB) disease.

In January, 2013, 4CMenB was licensed in Europe on immunogenicity and safety studies only. The vaccine induces bactericidal antibodies that target the respective antigens, which could be absent or variably expressed on the surface of different meningococci. Because 4CMenB contains multiple recombinant proteins in addition to the outer membrane vesicle, antibody concentrations or bactericidal activity against individual vaccine antigens do not reliably predict in-vitro killing of meningococci. For this reason, the Meningococcal Antigen Typing System (MATS) was developed to screen large numbers of meningococcal strains and predict whether they would be killed by 4CMenB-induced antibodies. MATS is a qualitative and quantitative ELISA that quantifies expression of the vaccine-associated antigens (fHbp, NHBA, and NadA) in combination with the ability of 4CMenB-induced antibodies to recognise these proteins on the surface of individual meningococcal isolates. For an isolate to be MATS positive, antibodies against at least one vaccine antigen must exceed the positive bactericidal threshold, which is assigned on the basis of killing using postvaccination sera from infants after their 12-month booster, or the isolate must possess homologous PorA (P1.4). In England and Wales, MATS predicted that 73% (95% CI 57–87%) of invasive MenB disease isolates in 2007–08 would be killed by vaccine-induced antibodies in infants. In a serum bactericidal antibody assay with human complement (hSBA), however, pooled sera from infants and adolescents immunised with 4CMenB killed 88% of a representative sample of MenB disease isolates from England and Wales during 2007–08. In the cost-effectiveness analysis, therefore, 4CMenB was predicted to protect against 73–88% of circulating MenB strains in the UK.

Compared with adolescents and adults, infants have lower cross-protection against MenB strains that are predicted by MATS to be non-vaccine preventable. Data from a recent university-associated MenB outbreak in the USA showed that sera from a third of 499 adolescents who received two doses of 4CMenB 10 weeks apart were unable to kill the outbreak strain using the hSBA assay, even though the outbreak strain was predicted by MATS to express two vaccine antigens.

Added value of this study

The UK is the first country to introduce 4CMenB into a publicly funded, national immunisation programme. In England, vaccine coverage was high in all eligible cohorts, reaching 95·5% for one dose and 88·6%% for two doses. During the first 10 months of the programme, two-dose vaccine effectiveness of 82·9% against all MenB disease was equivalent to a vaccine effectiveness of 94·2% against vaccine-preventable MenB strains. By the end of June, 2016, MenB cases in vaccine-eligible infants had halved, irrespective of the infants' vaccination status or expected vaccine strain coverage.

Implication of all the available evidence

We have provided the first evidence of protection against group B meningococcal disease conferred by the novel, multicomponent 4CMenB vaccine in infants. While ongoing national surveillance will continue to monitor the longer-term impact of the programme, these findings represent a step forward in the battle against meningococcal disease and will help reassure that the vaccine protects against this deadly infection.

basis of immunogenicity and safety studies alone. 4CMenB induces high titres of bactericidal antibodies against the target vaccine antigens but, as yet, protection against invasive disease has not been shown.

Other countries have been reluctant to introduce 4CMenB into their national programmes because of the high price of the vaccine and the low incidence of MenB, leading to unfavourable health economic assessments, as well as uncertainties around strain coverage, vaccine safety, and effectiveness.[6–9] In March, 2014, the UK Joint Committee on Vaccination and Immunisation (JCVI) concluded that 4CMenB could be cost-effective,[10] with a reduced two-dose infant priming schedule.[11] After a year of negotiation with the vaccine manufacturer, an infant immunisation programme with 4CMenB was announced in March, 2015,[12] and the first infants were vaccinated on Sept 1, 2015. Here, we report the first estimates of effectiveness and the early impact of the programme in England.

Methods

Case ascertainment and follow-up

Public Health England (PHE) undertakes enhanced national surveillance of invasive meningococcal disease in England through a combination of clinical, public health, and laboratory reporting. The PHE Meningococcal Reference Unit (MRU) provides a national service for confirming, grouping, and characterising invasive meningococcal isolates.[13] The MRU also provides free PCR testing of clinical samples from patients with suspected invasive meningococcal disease across England. Consequently, case ascertainment has remained consistently high.[14] Laboratory-confirmed cases are followed up with PHE local Health Protection Teams (HPTs), general practitioners, and hospital clinicians to collect demographic data, vaccination history, clinical presentation, and outcome of infection.

PHE has legal permission, provided by Regulation 3 of The Health Service (Control of Patient Information)

Regulations 2002, to process patient confidential information for national surveillance of communicable diseases. This includes PHE's responsibility to monitor the safety and effectiveness of vaccines, and as such, individual patient consent is not required.

Vaccine effectiveness

Vaccine effectiveness was estimated for vaccine-eligible infants (born on or after May 1, 2015) with laboratory-confirmed invasive MenB disease diagnosed between Sept 1, 2015, and June 30, 2016. If 4CMenB was protecting infants from MenB disease, then the proportion of vaccinated MenB cases would be expected to be lower than the proportion vaccinated in the comparator groups. The comparator group included all children in England who were eligible for the vaccine; this is known as the screening method.[15] Vaccine effectiveness is calculated as:

$$1 - \frac{\frac{PCV}{1 - PCV}}{\frac{PPV}{1 - PPV}}$$

where PCV is the proportion of vaccinated MenB cases and PPV is the vaccine coverage in age-matched infants across England (the comparator cohort).

As part of the national immunisation programme, infants were invited by their general practitioners for routine vaccinations at age 8 weeks, 12 weeks, and 16 weeks. Vaccine coverage increased exponentially during the week after infants became eligible (figure 1). To avoid this period with rapidly increasing coverage and to allow 2 weeks for development of an adequate immune response after vaccination, vaccine effectiveness for at least one dose was estimated using cases aged 77 days (11 weeks of age) or older and for two doses using cases aged 133 days (17 weeks of age) or older. Doses were discounted if MenB disease was diagnosed within 14 days of vaccination; therefore, an infant who developed MenB disease 5 days after the second dose of 4CMenB would be considered to have received a single dose of vaccine in the analysis.

Population vaccine coverage in England was obtained from ImmForm, an online system used by PHE to collect vaccine coverage for some national immunisation programmes. Monthly data are automatically uploaded by general practice information technology suppliers for each cohort reaching 26 weeks of age in the survey month. The denominator is the number of infants who, in the survey month, reach 26 weeks of age, and numerators are the number of infants in the denominator who received the first and the second dose of 4CMenB between 8–26 weeks of age.[16] To control for any confounding by age and time, for each MenB case, vaccine coverage was estimated for all infants in England who were born in the same month and at an age in days exactly 14 days younger than the age of the case on the specimen date (the comparator group). Because Immform does not collect individual dates of births or dates of vaccination, vaccine coverage for comparators was estimated by adjusting the 6-month ImmForm coverage using actual dates of birth and dates of vaccination for about 36 000 infants receiving their first dose and about 26 000 receiving their second dose, as supplied by five Child Health Information Systems (CHIS) in different geographical areas across England (appendix p 1).

See Online for appendix

To estimate two-dose vaccine effectiveness, those who developed MenB disease after only one dose were excluded. Two dose vaccine coverage was also adjusted to exclude those partially vaccinated and was calculated as:

$$\text{Adjusted coverage} = \frac{\text{2 dose coverage}}{\text{1 – coverage of exactly 1 dose}}$$

Vaccine impact

Vaccine impact was estimated for vaccine-eligible MenB cases (born on or after May 1, 2015, aged 10 weeks or older and diagnosed between Sept 1, 2015, and June 30, 2016) as described below (table). Incidence rate ratios (IRRs) were estimated for vaccine-eligible cases compared with cases diagnosed in the equivalent time period during the 4 years before vaccine introduction. Within the vaccine-eligible cohort, IRRs were also specifically calculated for the catch-up cohort (infants born in May or June, 2015), the routine cohort eligible for the first dose (born on or after July 1, 2015, with MenB disease at age 10–17 weeks), and for both doses (born on or after July 1, 2015, with MenB disease at age 18 weeks or older). To take into account possible changes over time in the absence of MenB vaccination, these IRRs were then adjusted using changes in incidence in all children aged younger than 5 years with MenB disease who were not in the vaccine-eligible or equivalent cohorts for the same time periods as those above. The ratios of the IRRs between the vaccine-eligible and ineligible cohorts were calculated using a Poisson regression model, which allowed calculation of 95% CIs for the IRR ratio. An interrupted time-series model was then fitted to 4 years of prevaccine data for each of the vaccine-eligible cohorts and to 5 years (4 prevaccine years plus the current year) for the vaccine-ineligible cohorts. Poisson regression was used to estimate an overall trend, with a factor for each of the individual cohorts. Vaccine impact was then estimated by comparing the 2015–16 data in vaccine-eligible cohorts with that predicted by the overall trend analysis.

For **ImmForm** see https://www.gov.uk/government/collections/immform

For the Poisson regression models, to assess model fit, the residual deviance and degrees of freedom were assessed by a χ^2 test. The main difference between the adjusted IRR estimates and the interrupted time-series model is that the latter assumes a common underlying

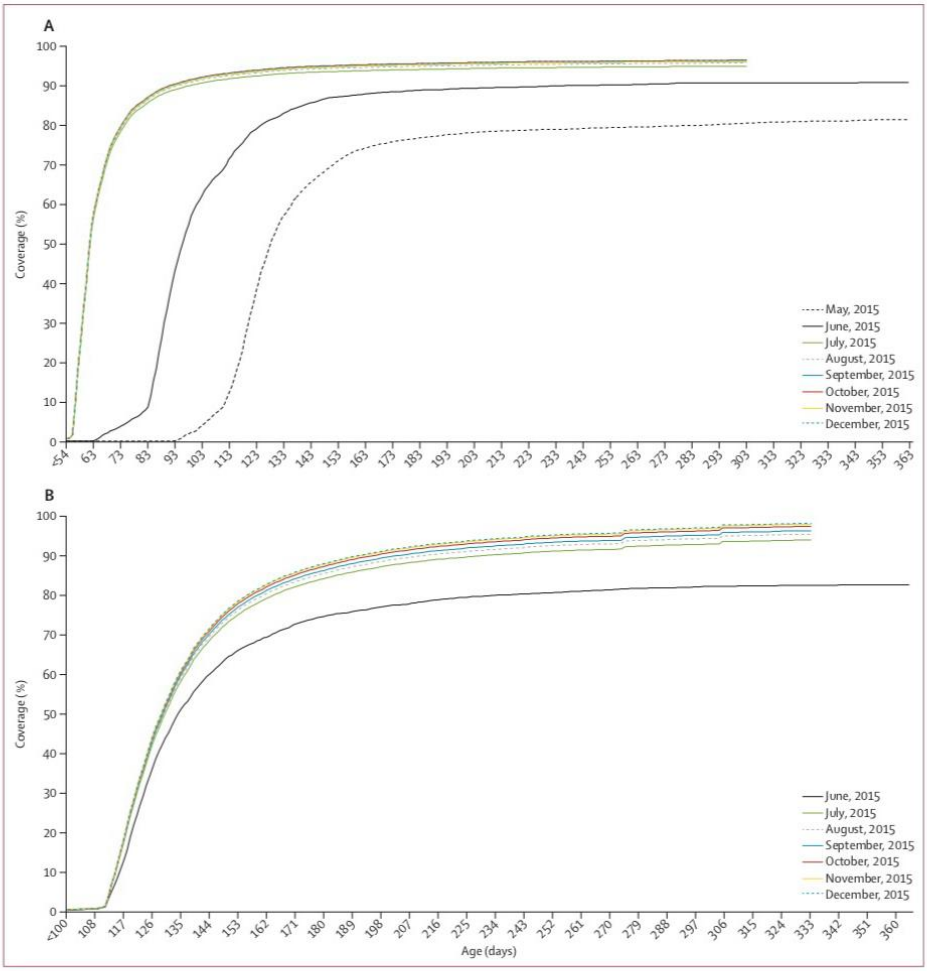

Figure 1: **Population coverage estimates for 4CMenB vaccine in England by age in days and month of birth for (A) dose 1 and (B) dose 2**
Coverage estimates are for infants born between May 1, 2015, and Dec 31, 2015, and immunised after vaccine introduction on Sept 1, 2015. Infants born in May, 2015, were only eligible for a single dose of vaccine at 4 months of age. 4CMenB=multicomponent group B meningococcal vaccine.

trend whereas the former assumes that the year-to-year changes were similar within age cohorts but not necessarily as a trend.

Role of funding source

The authors had sole responsibility for the study design, data collection, data analysis, data interpretation, and writing of the report. The authors are all employed by Public Health England, the study funder, which is a public body and an executive agency of the Department of Health. The corresponding author had full access to all the data and final responsibility for the decision to submit for publication.

Results

In England, introduction of 4CMenB rapidly achieved high vaccine coverage; in the routine cohort, vaccine coverage by birth month ranged between 94·8–95·5% for one dose and 84·8–88·6% for two doses by 6 months of age (figure 1; appendix p 2). Coverage for the catch-up cohort born in June, 2015, was 88·8% for one dose and 75·2% for two doses, and,

	Cases (Sept, 2015–June, 2016)	Comparison of the September to June period of the 4 prevaccine years (2011–12 to 2014–15)			Trend model	
		Cases in equivalent prevaccine cohorts (mean count per year)	IRR (95% CI), p value	Impact estimate as relative IRR (95% CI), p value	Cases in equivalent cohorts as predicted by the trend model	Impact estimate as trend model IRR (95% CI), p value*
Catch-up (born May 1–June 30, 2015)	9	24·75	0·36 (0·18–0·72), 0·004	0·42 (0·21–0·85), 0·016	19·4	0·46 (0·23–0·93), 0·029
Two-dose routine (born on or after July 1, 2015, aged ≥18 weeks)	18	33·75	0·53 (0·33–0·87), 0·012	0·62 (0·37–1·04), 0·07	26·4	0·68 (0·41–1·13), 0·134
One-dose routine (born on or after July 1, 2015, aged 10–17 weeks)	10	15·25	0·66 (0·34–1·28), 0·216	0·76 (0·38–1·52), 0·439	11·9	0·84 (0·43–1·65), 0·606
All vaccine-eligible cohorts combined	37	73·75	0·50 (0·36–0·71), 0·0001	0·58 (0·40–0·85), 0·005	57·8	0·64 (0·45–0·92), 0·015
Comparator (aged <5 years with MenB disease and excluding vaccine-eligible and equivalent prevaccine cohorts)	173	201	0·86 (0·73–1·01), 0·073			

IRR=incidence rate ratio. MenB=group B meningococcal disease. 4CMenB=multicomponent group B meningococcal vaccine. *Based on a common trend fitted to all data including comparator cohorts.

Table: **Numbers of laboratory confirmed MenB cases for five comparable annual time periods in England in cohorts eligible and non-eligible for 4CMenB vaccination and estimates of vaccine impact from different comparison models**

for the May, 2015, cohort, was 76·6% for the single dose that they were eligible for.

Between Sept 1, 2015, and June 30, 2016 (10 months), 55 cases of laboratory-confirmed invasive meningococcal disease were reported in vaccine-eligible infants (born on or after May 1, 2015, aged ≥10 weeks at diagnosis), including 37 (67%) cases with MenB, 11 (20%) with MenW, five (9%) with MenY, and two (4%) who were ungrouped due to low colony forming units in the submitted clinical samples. Most infants with MenB disease (27 [73%] of 37) were confirmed by PCR only, six by culture only (16%) and four (11%) by both methods. 15 (41%) of the 37 MenB cases had meningitis, 13 (35%) had septicaemia, and seven (19%) had both meningitis and septicaemia, while two (5%) had other clinical presentations. One child died aged 15 weeks and had received one 4CMenB dose 7 weeks before disease onset.

Of the 37 cases of MenB, four (11%) were among infants born in May, 2015 (two unvaccinated, one after a single dose, and one who inadvertently received two doses) and five (14%) in June, 2015 (two unvaccinated and three after one dose). The remaining 28 cases of MenB were eligible for routine vaccination; two were unvaccinated, 17 had received one dose, and nine had received two doses of 4CMenB. No evidence of temporal or geographical clustering of cases was noted in vaccinated infants who developed disease across the age range (25–44 weeks at diagnosis). None of the unvaccinated children had contraindications to receiving 4CMenB.

Three vaccinated infants, all in the routine cohort, developed disease within 14 days of their first (at 2 days and 4 days) or second (at 10 days) dose of 4CMenB and were classified as being unvaccinated and having had a single dose, respectively. Of the eight infants classified as unvaccinated, four were not eligible for two doses of 4CMenB; two because they were born in May and two because they were diagnosed before they were due their second dose.

For the two-dose vaccine effectiveness analysis, eight of the nine cases of MenB in the routine cohort (the infant who developed disease within 10 days of the second dose was excluded), one infant born in late May, who had inadvertently received two 4CMenB doses and four unvaccinated infants were included. The infant born in May was matched with vaccine coverage for infants born in June. The average matched vaccine coverage for the two-dose cohort across England was 92·9% and estimated vaccine effectiveness was 82·9% (95% CI 24·1–95·2).

The one-dose vaccine effectiveness analysis included 20 infants who had received a single dose (including one who developed disease 10 days after the second dose) and eight unvaccinated infants (including the two infants who developed disease 2 days and 4 days after the first dose). The average matched coverage for the one-dose cohort across England was 76·2% and estimated vaccine effectiveness was 22·0% (95% CI –105 to 67·1). For at least one dose of 4CMenB, the average matched coverage was 91·0% and estimated vaccine effectiveness was 64·0% (95% CI 8·9–84·0).

Cases of MenB in the different vaccine-eligible and comparator cohorts are shown in the table. Compared with their peers matched by age and time period for the 4 prevaccine years, a 50% reduction (IRR 0·50 [95% CI 0·36–0·71]; p=0·0001) in MenB cases was noted in the vaccine-eligible cohort compared with a non-significant 14% reduction in the unvaccinated cohort (table). Adjustment for this 14% disease reduction

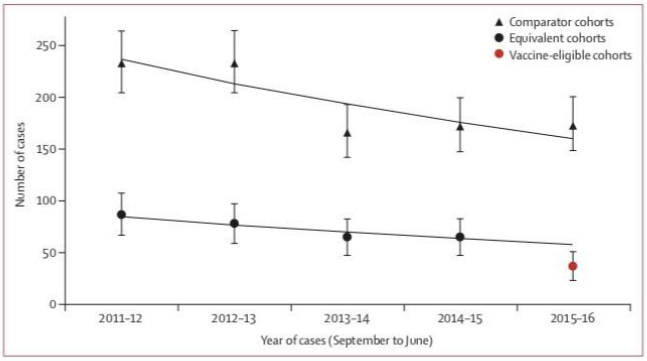

Figure 2: **Numbers of cases of MenB disease in vaccine-eligible and comparator cohorts in England, 2011–16, with Poisson 95% CIs and fitted trend**
The vaccine-eligible cohort included infants born on or after May 1, 2015, aged 10 weeks or older and diagnosed between Sept 1, 2015, and June 30, 2016. The equivalent cohorts fulfilled the same criteria as the vaccine-eligible cohorts for each of the previous 4 prevaccine years. The comparator cohorts included all children aged younger than 5 years with MenB disease excluding the vaccine-eligible and equivalent cohorts. MenB=group B meningococcal disease.

in the comparator cohort gave an estimated 42% reduction (relative IRR 0·58 [95% CI 0·40–0·85]; p=0·005) in the vaccine-eligible cohort. The greatest impact was noted in the catch-up cohort (58% relative reduction), with a 38% relative reduction in the routine cohort old enough to have received two 4CMenB doses and 24% in infants in the routine cohort who developed disease during a period when they could have been protected by their first dose (MenB disease at 10–17 weeks). Analysis using the prevaccine trends model estimated a slightly lower vaccine impact, with a 36% overall reduction in cases (table; figure 2). There was no evidence of lack of fit based on residual deviance and degrees of freedom (p=0·28 for non-trend model and p=0·18 for trend model), thus providing assurance that trends in MenB disease were consistent in the different age cohorts in recent years.

Discussion

A reduced two-dose infant priming schedule of the novel, multicomponent, protein-based 4CMenB vaccine was 82·9% effective in preventing MenB disease in infants aged younger than 12 months. During the first 10 months of the programme, cases of MenB halved in vaccine-eligible infants, providing further evidence of vaccine efficacy. This measure of impact does not take into account the vaccination status of the infants or whether the infecting MenB strain was vaccine preventable. The findings are robust, with similar results even after adjustment for disease trends in the 4 years before vaccine introduction and in non-vaccine eligible children.

4CMenB was licensed on immunogenicity and safety data only without an efficacy trial and with the knowledge that not all strains of MenB would be covered by the vaccine. 4CMenB targets proteins which, unlike the polysaccharide capsule, could be present or absent on the surface of meningococci. Each protein also varies in the degree of surface expression and the extent to which vaccine-induced antibodies recognise and bind these proteins. To predict MenB strain coverage by 4CMenB-induced antibodies, the Meningococcal Antigen Typing System (MATS)—a qualitative and quantitative ELISA for expression of fHbp, NHBA, and NadA—was developed.[17] A strain is considered to be vaccine preventable if MATS-positive for any of the three antigens or if the strain harbours PorA P1.4.

The MATS assay provides a conservative estimate of strain coverage and, in 2007–08, predicted that 73% of MenB isolates from patients with invasive meningococcal disease in England and Wales would be killed by pooled post-vaccination sera.[18] The serum bactericidal antibody assay with human complement (hSBA) using pooled post-immunisation infant sera, however, predicted 88% coverage against a diverse panel of MenB strains from patients in England and Wales.[19] With differing strain coverage estimates, uncertainties surrounding the vaccine's effectiveness grew when, in a recent university outbreak in the USA, sera from a third of 499 participants who received two doses of 4CMenB were unable to kill the outbreak strain in hSBA,[20] despite this strain being predicted by MATS to express two vaccine antigens (fHbp and NHBA). In infants, the protection offered by 4CMenB is expected to be lower because, compared with adolescents, they are less likely to mount cross-protective antibodies against strains with unmatched vaccine antigens.[21]

The health economic model that was cost-effective assumed a two-dose infant priming schedule, 88% MenB strain coverage and 95% vaccine efficacy against the vaccine-preventable strains, with a potential to prevent a quarter (26%) of all meningococcal cases in the first 5 years of the programme.[11] Our results are remarkably aligned with the model. If, as predicted by hSBA, 88% of MenB strains were covered by 4CMenB,[20] then the vaccine effectiveness against vaccine-preventable strains would be 94·2%. Although the CIs for the vaccine effectiveness of the two-dose regimen are wide because of small numbers of cases, the estimates are significant and findings are supported by the impact analysis showing a significant reduction in cases of MenB in vaccine-eligible infants. The lower and non-significant vaccine effectiveness after one dose was expected because a single dose of vaccine is poorly immunogenic in infants.[22,23] These results, however, will require confirmation through long-term surveillance. An important observation, even with the small number of cases, was the large proportion of cases (50%, 10/20) in the routine cohort who developed MenB disease after 16 weeks, the age at which they would have become eligible for their second 4CMenB, and thus might potentially have been prevented through timely vaccination.

The analysis that adjusted for historic trends suggested a lower impact in vaccine-eligible cohorts because this was less affected by the increase in cases of MenB in the

non-eligible cohorts during 2015–16. In both analyses, a higher impact was observed in the catch-up cohort, despite the opportunistic schedule of one or two doses and lower vaccine coverage than the routine cohort. This cohort completed their recommended vaccinations before the meningococcal season when they would have reached the peak age for disease. By contrast, vaccine impact in the routine cohort would have been diluted by accumulation of younger infants who were being immunised throughout the surveillance period. Follow-up of cases through to the next meningococcal season should provide more robust estimates of vaccine effectiveness and impact for the routinely vaccinated cohorts.

In England, enhanced national surveillance has been in place for more than two decades;[2] the provision of a national reference laboratory, use of multiple data sources, and the support provided by public health and UK National Health Service staff ensures consistently high case ascertainment, allowing reliable assessment of trends over time. We also achieved very high vaccine coverage in the routine and the catch-up cohorts as soon as the programme was implemented,[24,25] despite initial concerns about high rates of postvaccination fever and national recommendations to routinely offer prophylactic paracetamol with 4CMenB.[1] Consequently, we have been able to measure vaccine effectiveness and impact 1 year after the programme was introduced. In view of the uncertainties associated with this novel vaccine and the recent publication reporting seroprotection in only two-thirds of immunised adolescents,[20] we hope our early results will reassure clinicians, immunisers, and policy makers that the vaccine is effective in infants, even with a reduced two-dose priming schedule. A major limitation that is unlikely to be overcome is that 70% of cases of MenB in vaccine-eligible infants were confirmed by PCR only and the MATS assay requires culture isolates to assess strain coverage. MATS is also only currently validated for MenB and, therefore, assessment of impact of 4CMenB on the other meningococcal capsular groups will be challenging.

Our initial results show a significant reduction in cases of MenB among vaccine-eligible infants within 10 months of introduction of 4CMenB into the UK. Although the vaccine is licensed using a three-dose priming schedule in infancy, short-term vaccine effectiveness against MenB disease was high after two doses. Ongoing national surveillance will continue to monitor the long-term impact of the programme on disease burden alongside vaccine safety and disease severity in young children.

Contributors

SRP, KB, HC, and SR were responsible for the epidemiological surveillance data. KB, CW, and JMW collected and contributed vaccine coverage data. SRP and NJA did the data analysis and prepared the figures. SRP and SNL did the literature search and wrote the first draft of the report. SRP, NJA, MER, RB, and SNL contributed to the data interpretation. All authors commented on the drafts of the paper and agreed with the final draft of the report.

Acknowledgments

We thank local Health Protection Teams, Child Health Record Departments, and General Practitioners for their contribution to ascertaining vaccination statuses; and are also grateful to Kim Taylor, Tracy Smeulders, and Rehana Shivji for clinical follow-up and data entry.

Declaration of interests

SNL and RB do contract research for vaccine manufacturers (including GSK, Pfizer, and Sanofi Pasteur) on behalf of St George's University of London and Public Health England (London, UK), respectively, but receive no personal remuneration. The Immunisation, Hepatitis, and Blood Safety Department has provided GSK with postmarketing surveillance reports on meningococcal, *Haemophilus influenzae*, and pneumococcal infections, which the companies are required to submit to the UK Licensing Authority in compliance with their Risk Management Strategy. A cost recovery charge is made for these reports. NJA declares no competing interests.

References

1 Ladhani SN, Ramsay M, Borrow R, Riordan A, Watson JM, Pollard AJ. Enter B and W: two new meningococcal vaccine programmes launched. *Arch Dis Child* 2016; **101:** 91–95.
2 Campbell H, Borrow R, Salisbury D, Miller E. Meningococcal C conjugate vaccine: the experience in England and Wales. *Vaccine* 2009; **27:** B20–29.
3 Campbell H, Saliba V, Borrow R, Ramsay M, Ladhani SN. Targeted vaccination of teenagers following continued rapid endemic expansion of a single meningococcal group W clone (sequence type 11 clonal complex), United Kingdom 2015. *Euro Surveill* 2015; **20:** 28.
4 Tan LK, Carlone GM, Borrow R. Advances in the development of vaccines against Neisseria meningitidis. *N Engl J Med* 2010; **362:** 1511–20.
5 Serruto D, Bottomley MJ, Ram S, Giuliani MM, Rappuoli R. The new multicomponent vaccine against meningococcal serogroup B, 4CMenB: immunological, functional and structural characterization of the antigens. *Vaccine* 2012; **30:** B87–97.
6 Tirani M, Meregaglia M, Melegaro A. Health and economic outcomes of introducing the new MenB vaccine (Bexsero) into the Italian Routine Infant Immunisation Programme. *PLoS One* 2015; **10:** e0123383.
7 Vernikos G, Medini D. Bexsero(R) chronicle. *Pathog Glob Health* 2014; **108:** 305–16.
8 Yamashiro H, Cutcliffe N, Dobson S, Fisman D, Gold R. The role of pediatricians as key stakeholders in influencing immunization policy decisions for the introduction of meningitis B vaccine in Canada: The Ontario perspective. *Can J Infect Dis Med Microbiol* 2015; **26:** 183–90.
9 Meeting of the Advisory Committee on Immunization Practices (ACIP). Centers for Disease Control and Prevention, 2015. http://www.cdc.gov/vaccines/acip/meetings/downloads/agenda-archive/agenda-2015-06.pdf (accessed Aug 16, 2016).
10 Joint Committee on Vaccination and Immunisation. JCVI position statement on use of Bexsero meningococcal B vaccine in the UK, 2014. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/294245/JCVI_Statement_on_MenB.pdf (accessed Aug 8, 2016).
11 Christensen H, Trotter CL, Hickman M, Edmunds WJ. Re-evaluating cost effectiveness of universal meningitis vaccination (Bexsero) in England: modelling study. *BMJ* 2014; **349:** g5725.
12 Piggot M. Meningitis vaccine for every new UK baby announced by health secretary Jeremy Hunt. International Business Times, March 29, 2015. http://www.ibtimes.co.uk/meningitis-vaccine-every-new-uk-baby-announced-by-health-secretary-jeremy-hunt-1494025 (accessed Aug 8, 2016).
13 Public Health England. Meningococcal Reference Unit-User Manual. Public Health England, 2015. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/472708/MRU_User_Manual_FINAL.pdf (accessed Aug 15, 2016).
14 Ladhani SN, Waight PA, Ribeiro S, Ramsay ME. Invasive meningococcal disease in England: assessing disease burden through linkage of multiple national data sources. *BMC Infect Dis* 2015; **15:** 551.
15 Farrington CP. Estimation of vaccine effectiveness using the screening method. *Int J Epidemiol* 1993; **22:** 742–46.

16 Public Health England. Provisional vaccine coverage estimates for the new meningococcal B (MenB) immunisation programme for England. Public Health England, 2016. https://www.gov.uk/government/publications/meningococcal-b-immunisation-programme-vaccine-coverage-estimates (accessed Aug 15, 2016).

17 Donnelly J, Medini D, Boccadifuoco G, et al. Qualitative and quantitative assessment of meningococcal antigens to evaluate the potential strain coverage of protein-based vaccines. *Proc Natl Acad Sci USA* 2010; **107:** 19490–95.

18 Vogel U, Taha MK, Vazquez JA, et al. Predicted strain coverage of a meningococcal multicomponent vaccine (4CMenB) in Europe: a qualitative and quantitative assessment. *Lancet Infect Dis* 2013; **13:** 416–25.

19 Frosi G, Biolchi A, Lo Sapio M, et al. Bactericidal antibody against a representative epidemiological meningococcal serogroup B panel confirms that MATS underestimates 4CMenB vaccine strain coverage. *Vaccine* 2013; **31:** 4968–74.

20 Basta NE, Mahmoud AAF, Wolfson J, et al. Immunogenicity of a meningococcal B vaccine during a university outbreak. *N Engl J Med* 2016; **375:** 220–28.

21 Brunelli B, Del Tordello E, Palumbo E, et al. Influence of sequence variability on bactericidal activity sera induced by Factor H binding protein variant 1.1. *Vaccine* 2011; **29:** 1072–81.

22 Cartwright K, Morris R, Rumke H, et al. Immunogenicity and reactogenicity in UK infants of a novel meningococcal vesicle vaccine containing multiple class 1 (PorA) outer membrane proteins. *Vaccine* 1999; **17:** 2612–19.

23 Torres F, Safadi M, Martinez A, et al. Immunogenicity and safety of a 2 or 3 dose primary series of meningococcal serogroup b vaccine in infants, and a 2-dose catch-up series in children. 34th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID); Brighton. UK: ESPID; 2016: ESP16-0464.

24 Public Health England. Preliminary vaccine coverage estimates for the new meningococcal B (MenB) immunisation programme for England, update to the end of April 2016. Public Health England, 2016. https://www.gov.uk/government/publications/meningococcal-b-immunisation-programme-vaccine-coverage-estimates (accessed Oct 24, 2016).

25 Public Health England. Provisional vaccine coverage estimates for the new meningococcal B (MenB) immunisation programme for England, January 2016. Public Health England, 2016. https://www.gov.uk/government/publications/meningococcal-b-immunisation-programme-vaccine-coverage-estimates (accessed Aug 4, 2016).

Study 5: Vaccination of Infants with Meningococcal Group B Vaccine (4CMenB) in England *The New England Journal of Medicine* (2020)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 23, 2020 VOL. 382 NO. 4

Vaccination of Infants with Meningococcal Group B Vaccine (4CMenB) in England

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ABSTRACT

BACKGROUND

In September 2015, the United Kingdom introduced the multicomponent meningococcal group B vaccine (4CMenB, Bexsero) into its publicly funded national immunization program at a reduced two-dose priming schedule for infants, with a 12-month booster.

METHODS

Using data from enhanced national surveillance of invasive meningococcal disease in England, we evaluated the effect of vaccination on the incidence of meningococcal group B disease during the first 3 years of the program. The effect of vaccination was assessed by comparing the observed incidence of disease with the expected incidence based on the incidence during the 4-year prevaccination period in equivalent cohorts and with the use of disease trends in cohorts of children younger than 5 years of age who were not eligible to receive the vaccine. Vaccine effectiveness was estimated with the use of the indirect screening method.

RESULTS

4CMenB uptake in England remained consistently high; data from the first 3 months of 2018 showed that 92.5% of children had completed the primary immunizations by their first birthday and 87.9% had received all three doses by 2 years. From September 2015 through August 2018, the incidence of meningococcal group B disease in England (average annual birth cohort, approximately 650,000 infants) was significantly lower in vaccine-eligible cohorts than the expected incidence (63 observed cases as compared with 253 expected cases; incidence rate ratio, 0.25; 95% confidence interval [CI], 0.19 to 0.36), with a 75% reduction in age groups that were fully eligible for vaccination. The adjusted vaccine effectiveness against meningococcal group B disease was 52.7% (95% CI, −33.5 to 83.2) with a two-dose priming schedule for infants and 59.1% (95% CI, −31.1 to 87.2) with a two-dose priming schedule plus a booster at 1 year). Over the 3-year period, there were 169 cases of meningococcal group B disease in the vaccine-eligible cohorts, and an estimated 277 cases (95% CI, 236 to 323) were prevented.

CONCLUSIONS

The 4CMenB program was associated with continued positive effect against meningococcal group B disease in children in England, and protection after three doses of the vaccine was sustained for at least 2 years. (Funded by Public Health England.)

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N Engl J Med 2020;382:309-17.
DOI: 10.1056/NEJMoa1901229

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Neisseria meningitidis, a major cause of meningitis and septicemia throughout the world, is associated with considerable morbidity and mortality. Twelve different meningococcal capsular groups are recognized, of which six (A, B, C, W, X, and Y) are responsible for most cases of invasive meningococcal disease. In Europe, meningococcal group B is responsible for most cases of childhood meningococcal disease, although the incidence of this disease has declined over the past decade.[1] Polysaccharide–protein conjugate vaccines have been effective in preventing meningococcal disease caused by capsular groups A, C, W, and Y because of the direct protection and indirect (herd) protection through prevention of carriage acquisition among vaccinated adolescents.[2] The development of such a vaccine against meningococcal group B has been challenging because of the structural similarity of the meningococcal group B polysaccharide capsule with polysialic acid structures on human neuronal cells, which results in poor immunogenicity.[3]

In January 2013, a protein-based, multicomponent vaccine against meningococcal group B (4CMenB, Bexsero, GlaxoSmithKline Biologicals) was licensed in Europe at a three-dose priming schedule for infants, followed by a booster in the second year of life. The vaccine includes three recombinant proteins (factor H–binding protein [FHbp] peptide 1 [variant 1], neisserial heparin-binding antigen [NHBA] peptide 2, and neisseria adhesin A [NadA] peptide 8 [variant NadA-2/3]), along with PorA P1.4–containing outer-membrane vesicles from the New Zealand outbreak strain. This vaccine was licensed on the basis of safety and immunogenicity studies only, without real-world evidence of protection against invasive disease.

The Meningococcal Antigen Typing System (MATS) was developed to predict strain coverage by 4CMenB. It comprises genotypic characterization of PorA in conjunction with a qualitative and quantitative enzyme-linked immunosorbent assay to quantify FHbp, NHBA, and NadA expression in combination with their recognition by 4CMenB-induced antibodies on individual meningococcal isolates. This assay can be performed only on culture isolates and not on specimens obtained from patients with disease confirmed by nonculture methods such as the polymerase-chain-reaction (PCR) test only.[4] The MATS estimated 73% strain coverage in England and Wales before the introduction of 4CMenB.[5]

In September 2015, the United Kingdom became the first country to offer 4CMenB to all infants free of charge. The vaccine is offered at 8 and 16 weeks of age, with a booster at 12 months. At the start of the program, an opportunistic catch-up vaccination was also offered to children at 12 and 16 weeks of age at their routine immunization visits. Within 10 months after the program began, cases of meningococcal group B disease in infants who were eligible to receive the vaccine had nearly halved, and the effectiveness of two doses of vaccine was 82.9% (95% confidence interval [CI], 24.1 to 95.2) against all cases of laboratory-confirmed invasive meningococcal group B disease in infants.[6] In 2016, the first infants who received the primary immunizations became eligible for the 12-month booster. Here, we report the effect and effectiveness of 4CMenB with regard to invasive meningococcal group B disease in infants and children at 1 year of age and 2 years of age after the first 3 years of the national immunization program in England.

METHODS

DISEASE SURVEILLANCE AND VACCINE UPTAKE

Public Health England conducts enhanced national surveillance for invasive meningococcal disease in England.[6] Briefly, hospital laboratories routinely submit isolates obtained from patients with invasive meningococcal disease to the Meningococcal Reference Unit of Public Health England for confirmation and serogrouping. Since 2014, all isolates of invasive meningococcal group B have undergone testing with the MATS.[6] The Meningococcal Reference Unit also provides a free meningococcal PCR testing service for patients with suspected meningococcal disease across England, and the Immunisation and Countermeasures Division at Public Health England provides public health and vaccination advice for individual patients and supports the investigation and management of suspected clusters and outbreaks. As a result of the multiple data sources used for surveillance, case ascertainment has remained consistently high across all age groups.[7,8] Public Health England routinely collects data on the vaccination history, risk factors, clinical presentations, and outcomes of all

patients with invasive meningococcal disease. Full details of the meningococcal surveillance plan in England are available at www.gov.uk/government/publications/meningococcal-disease-enhanced-surveillance-plan.

Data on vaccine uptake in England are routinely collected through primary care and child health information systems. In addition to reporting the percentage of eligible children who received two doses by 12 months and three doses by 18 months, the timing of vaccination in days of age was calculated with the use of individual-level data from local child health information systems (see the Supplementary Appendix, available with the full text of this article at NEJM.org).

STUDY DESIGN AND SUPPORT

The authors had sole responsibility for the study design; the data collection, analysis, and interpretation; and the writing of the manuscript. All the authors are employed by Public Health England, the study funder, which is a public body and an executive agency of the U.K. Department of Health. The first author had full access to all the data and final responsibility for the decision to submit the manuscript for publication.

STATISTICAL ANALYSIS

The population effect was estimated with the use of national surveillance data on cases of laboratory-confirmed meningococcal group B disease. We calculated the change in the incidence of the disease from 4 prevaccine surveillance years (September through the following August) to the first 3 complete years after 4CMenB was introduced. The age groups for the analysis were the following: 0 to 8 weeks (infants who were too young for vaccination), 9 to 17 weeks (part of this group was eligible for one 4CMenB dose in the 2015–2016 surveillance year, and the whole group was eligible for one 4CMenB dose in 2016–2017 and 2017–2018), 18 to 51 weeks (part of this group was eligible to receive two 4CMenB doses in 2015–2016, and the whole group was eligible in 2016–2017 and 2017–2018), 1 year (part of this group was eligible to receive three doses in 2016–2017, and the whole group was eligible to receive three doses in 2017–2018), 2 years (part of this group was eligible to receive three doses in 2017–2018), and 3 to 4 years (children who were too old to receive 4CMenB throughout the study period).

To estimate effect in each vaccine-eligible group, we initially estimated incidence rate ratios by comparing the numbers of cases of disease in each postvaccination surveillance year with those in the equivalent cohort during the 4 prevaccination years. To account for any changes over time that were unrelated to meningococcal group B vaccination, the incidence rate ratios were then adjusted for changes in the incidence of meningococcal group B disease in all children younger than 5 years of age who were not in the vaccine-eligible cohorts. This was possible because the meningococcal group B immunization program for infants does not provide any indirect protection to unvaccinated children. Full details regarding the Poisson models used for estimation of the incidence rate ratios and the predicted incidence in the absence of vaccination are provided in the Supplementary Appendix. Estimates of incidence rate ratios and 95% confidence intervals have not been adjusted for multiple comparisons, so inferences based on these intervals may not all be reproducible.

Vaccine effectiveness was estimated in children who were eligible to receive the vaccine through the routine program (i.e., those born on or after July 1, 2015) and who had laboratory-confirmed invasive meningococcal group B disease with an onset between September 1, 2015, and August 31, 2018. Children who were eligible for opportunistic vaccination (i.e., those who were born in May or June 2015) were excluded because their priming schedules were different and their vaccine uptake was not as well documented. Children were included if they were at least 77 days of age and younger than 13 months at the onset of disease (for estimates of the effectiveness of one dose), at least 133 days of age and younger than 13 months (for estimates of the effectiveness of two doses), and at least 365 days of age (for estimates of the effectiveness of three doses). Vaccine doses received by children with confirmed disease were counted if the onset occurred at least 14 days after the dose was received. The comparator group included all children who were eligible to receive 4CMenB in England.

If 4CMenB was protecting infants from meningococcal group B disease, then the percentage of vaccinated children with confirmed disease would be lower than the percentage of children who were vaccinated in the whole popu-

lation. The formula for vaccine effectiveness (VE) based on this screening method[9] is

$$VE = 1 - [PCV/(1 - PCV)]/[PPV/(1 - PPV)],$$

where PCV is the percentage of vaccinated children with meningococcal group B disease and PPV is the vaccine coverage in infants across England who were born in the same year and month and at an age in days exactly 14 days younger than the age of the child at disease onset (the comparator cohort for each individual child with the disease) (see the Supplementary Appendix). This 14-day period allows for an immune response to develop after vaccination. In order to use this age-matched and period-matched coverage for each child with disease, logistic regression was used with the vaccination status of the child as the binary outcome variable, only a constant fitted, and an offset for the log odds of the matched coverage. Vaccine effectiveness was calculated as 1 minus the odds ratio in the model. Vaccine effectiveness was assessed this way according to the number of doses: one primary dose with meningococcal group B disease diagnosed before 13 months of age; two primary doses with meningococcal group B disease diagnosed before 13 months of age; and the complete three-dose schedule with meningococcal group B disease diagnosed before 36 months of age. To estimate vaccine effectiveness according to the number of doses, the coverage for the equivalent number of doses in the population was used. Data were analyzed with the use of Stata software, version 14 (StataCorp).

Since 4CMenB does not protect against all meningococcal group B strains, the results of the MATS testing of isolates of invasive meningococcal group B obtained from vaccinated children were used to estimate the vaccine strain coverage of meningococci causing invasive disease in the different vaccinated cohorts. To estimate vaccine effectiveness against vaccine-preventable meningococcal group B strains only, the vaccine effectiveness against all meningococcal group B disease (vaccine effectiveness$_{all}$) was adjusted by applying the proportion (p) of culture-confirmed cases in vaccinated children that were MATS-positive to the total number of confirmed cases of meningococcal group B disease with MATS results in that cohort. The adjusted vaccine effectiveness (VE$_{mats}$) assumed no protection against MATS-negative strains. The following formula was used:

$$VE_{mats} = 1 - 1/\{1 + [1/p] \times [VE_{all}/(1 - VE_{all})]\}.$$

The derivation is provided in the Supplementary Appendix.

RESULTS

VACCINE UPTAKE

In England, 4CMenB uptake has remained consistently high since the vaccine was introduced into the national program in September 2015 (Fig. 1A). Data from the first 3 months of 2018 showed that 92.5% of children in England (average annual birth cohort, approximately 650,000 infants) had completed the primary immunizations by their first birthday and 87.9% had received all three doses by 2 years. In a representative sample of approximately 60,000 infants receiving the first dose, approximately 60,000 receiving the second dose, and approximately 30,000 receiving the booster in different geographic areas across England (see the Supplementary Appendix), the median age at 4CMenB vaccination was 61 days (interquartile range, 58 to 67) for the first dose, 128 days (interquartile range, 120 to 144) for the second dose, and 387 days (interquartile range, 377 to 407) for the booster (Fig. 1B).

EFFECT OF VACCINATION

The fitted model showed a 29% increase in the number of cases between 2013–2014 and 2017–2018, based on the observed number of cases of meningococcal group B disease in unvaccinated cohorts (P=0.11) (Fig. 2). The model for estimating effect showed no evidence of lack of fit (P=0.57), indicating that it was reasonable to assume that changes in cohorts of children who were not eligible to receive the vaccine because of age would have also occurred in the vaccine-eligible cohorts.

The estimates of adjusted incidence rate ratios show significant decreases in the incidence of meningococcal group B disease in all vaccine-eligible cohorts of children who received at least two doses of 4CMenB, including those in which only some of the group were eligible for vaccination (Table 1). In children who were 18 to 51 weeks of age, there were fewer cases of meningo-

coccal group B disease than expected for 3 consecutive years. In the second year of the program, fewer than expected cases were also observed in children who were 1 year of age and who became eligible for a three-dose schedule after July 2016. This cohort continued to benefit from vaccination in the third year of the program, with significantly fewer cases observed among children who were 2 years of age during 2017–2018 (Fig. 2).

When the age groups in which all children were eligible for vaccination were combined, the reduction in the incidence of meningococcal group B disease was 75% (63 observed cases as compared with 253 expected cases; incidence rate ratio, 0.25; 95% CI, 0.19 to 0.36), as compared with a reduction of 45% in the cohorts in which only some children were eligible (106 observed cases as compared with 193 expected cases; incidence rate ratio, 0.55; 95% CI, 0.43 to 0.70). The difference between the number of observed cases (169 cases) and expected cases (446 cases) of meningococcal group B disease in the vaccine-eligible cohorts was 277 (95% CI, 236 to 323) in the first 3 years of the program (i.e., 62% fewer cases than expected).

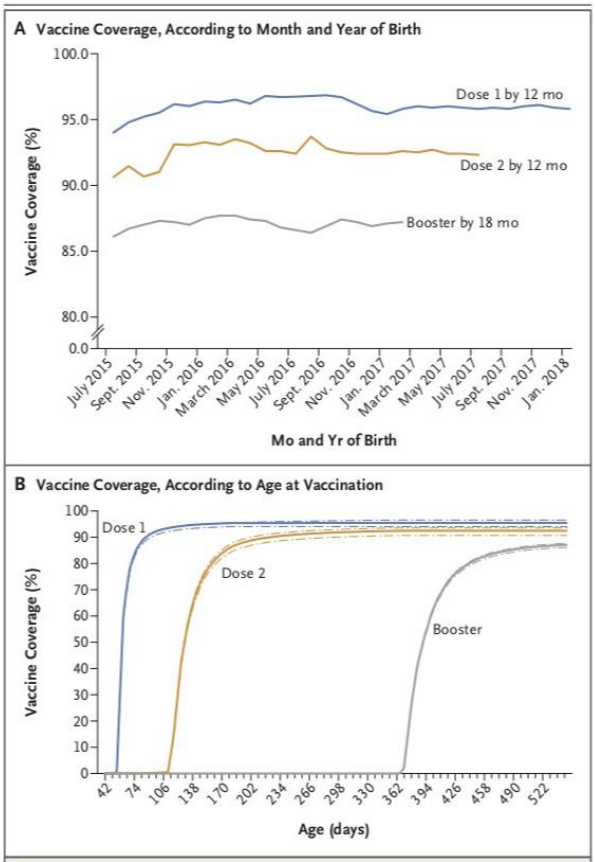

Figure 1. 4CMenB Vaccine Coverage, According to Recipients' Month and Year of Birth and Age at Vaccination.

Panel A shows vaccine coverage by 12 months for the first and second doses of the meningococcal group B vaccine (4CMenB), as well as uptake of the 12-month booster by 18 months of age. Panel B shows vaccination coverage according to age in days at the time of the first dose of the vaccine, the second dose, and the booster dose among infants born in the months with the lowest (July 2015, lower dashed line), median (January 2017, solid line), and highest (March 2016, upper dashed line) final vaccine coverage. The first dose was offered at 8 weeks of age, the second dose was offered at 16 weeks of age, and the booster dose was offered at 12 months.

VACCINE EFFECTIVENESS

Of the 187 children with meningococcal group B disease who were born after July 1, 2015, a total of 147 who were at least 77 days of age were eligible for the vaccine effectiveness analysis. The adjusted vaccine effectiveness for a single dose of 4CMenB was 24.1% (95% CI, −37.6 to 58.2) according to data on 74 children with disease (16 children who had not received the vaccine and 58 who had received one dose). Of the children with an onset of meningococcal group B disease between 133 days and 13 months of age, 4 were unvaccinated and 37 had received two doses of 4CMenB. Thus, the adjusted vaccine effectiveness was 52.7% (95% CI, −33.5 to 83.2). In this group, 26 children had disease that was confirmed by culture and, of these, 16 (62%) had MATS-positive disease. Assuming that only the MATS-positive strains were preventable by 4CMenB, the estimated vaccine effectiveness against vaccine-preventable meningococcal group B strains among children who received two doses was 64.4%.

Meningococcal group B disease developed in 29 infants who were eligible for the three-dose schedule, including 25 who had received the three recommended doses. The adjusted vaccine effectiveness among children who received three doses was 59.1% (95% CI, −31.1 to 87.2). Of the 12 isolates obtained from children with culture-confirmed disease, 7 (58%) were MATS-positive. The estimated vaccine effectiveness against vaccine-

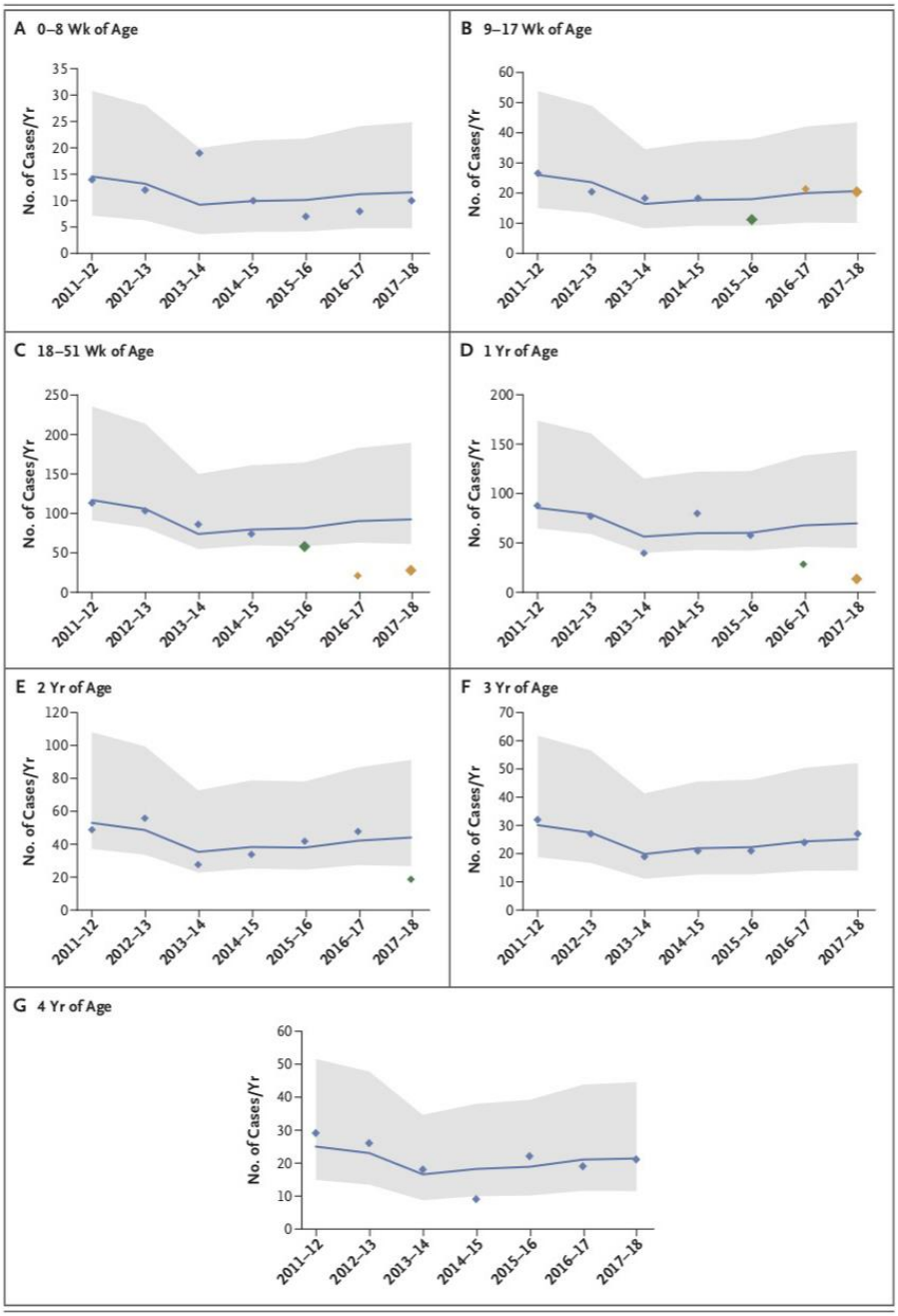
A 0–8 Wk of Age
B 9–17 Wk of Age
C 18–51 Wk of Age
D 1 Yr of Age
E 2 Yr of Age
F 3 Yr of Age
G 4 Yr of Age
No. of Cases/Yr
2011–12
2012–13
2013–14
2014–15
2015–16
2016–17
2017–18

Figure 2 (facing page). Number of Children with Meningococcal Group B Disease in Each Surveillance Year.

The orange diamonds indicate children who were fully eligible to receive the vaccine, the green diamonds those who were partially eligible to receive the vaccine, and the blue diamonds those in the comparator cohorts. The fitted prediction in the absence of vaccination (blue line) and its 95% prediction interval (gray region) are also shown. Data shown for each year are from September through August. Infants who were 8 weeks of age or younger (Panel A) were not eligible to receive the vaccine. Among infants who were 9 to 17 weeks of age (Panel B), some infants in 2015–2016 (green diamond) and all the infants in the 2016–2017 and 2017–2018 periods (orange diamonds) were eligible to receive one dose. Among infants who were 18 to 51 weeks of age (Panel C), some infants in 2015–2016 (green diamond) and all the infants in the 2016–2017 and 2017–2018 periods (orange diamonds) were eligible to receive two doses. Among children who were 1 year of age (Panel D), some children in 2016–2017 (green diamond) and all the children in 2017–2018 (orange diamond) were eligible to receive two priming doses plus a 12-month booster. Among children who were 2 years of age (Panel E), some children in 2017–2018 (green diamond) were eligible to receive two priming doses plus a 12-month booster. Children who were 3 and 4 years of age (Panels F and G) were not eligible to receive the vaccine.

preventable meningococcal group B strains among children who received three doses was 71.2%.

DISCUSSION

This study provides real-world evidence of the effectiveness of 4CMenB in preventing invasive meningococcal group B disease 3 years after its introduction into the U.K. national infant immunization program. Our analysis included all children with meningococcal group B disease in the vaccine-eligible cohorts, irrespective of vaccination status or strain coverage. We found that the 12-month booster protected against meningococcal group B disease for at least 2 years, which is reassuring given the initial concerns about rapidly waning levels of antibodies.[10] This is particularly important because the highest burden of meningococcal group B disease in England occurs during the first 3 years of life.[11] Our point estimates of vaccine effectiveness are consistent with the reduction in cases of meningococcal group B disease in each of the vaccine-eligible cohorts; the estimates of vaccine effectiveness have wide confidence intervals because of the small numbers of cases.

Table 1. Incidence of Meningococcal Group B Disease before and after the Vaccine Introduction Period.*

Age Group	Average Annual No. of Children with Disease, Prevaccination Period	No. of Children with Disease, Postvaccination Period			Incidence Rate Ratio (95% CI)†			Adjusted Incidence Rate Ratio (95% CI)‡			
	2010–2011 to 2014–2015	2015–2016	2016–2017	2017–2018	2015–2016 vs. 2010–2015	2016–2017 vs. 2010–2015	2017–2018 vs. 2010–2015	2015–2016 vs. 2010–2015	2016–2017 vs. 2010–2015	2017–2018 vs. 2010–2015
0–8 wk	13.75	7	8	10	0.52 (0.24–1.14)	0.60 (0.28–1.25)	0.75 (0.38–1.48)			
9–17 wk	20.50	11	21	20	0.55 (0.29–1.02)	1.05 (0.65–1.69)	1.01 (0.62–1.65)	0.62 (0.32–1.20)	1.07 (0.63–1.81)	0.99 (0.56–1.74)
18–51 wk	94.00	58	21	28	0.63 (0.48–0.83)	0.23 (0.15–0.35)	0.31 (0.21–0.45)	0.72 (0.52–0.99)	0.23 (0.14–0.38)	0.30 (0.19–0.49)
1 yr	71.25	58	29	14	0.83 (0.63–1.11)	0.42 (0.28–0.61)	0.20 (0.12–0.35)		0.43 (0.28–0.66)	0.20 (0.11–0.36)
2 yr	41.75	42	48	19	1.02 (0.73–1.43)	1.18 (0.85–1.62)	0.46 (0.29–0.75)			0.43 (0.25–0.74)
3 yr	24.75	21	24	27	0.83 (0.52–1.33)	0.97 (0.62–1.52)	1.11 (0.72–1.7)			
4 yr	20.50	22	19	21	1.04 (0.65–1.66)	0.90 (0.55–1.48)	1.02 (0.63–1.64)			

* Data shown for each year are from September through August, and the data are aggregated according to the surveillance year in which the specimen was obtained.
† These incidence rate ratios were adjusted only to account for changes in the population denominators.
‡ These incidence rate ratios were adjusted according to changes in the incidence of meningococcal B disease in the age cohorts of children who were not eligible to receive the vaccine.

The strength of this study lies in the consistently high vaccine uptake nationally and the near real-time enhanced national surveillance for all laboratory-confirmed cases, which is facilitated by the provision of a single national meningococcal reference unit. This surveillance allows for rapid assessment of vaccine effect and effectiveness at a national level. Our previous model, which used common trend lines for the expected cases,[6] did not fit the data after 2013–2014 because of an increase in cases of meningococcal group B disease in the cohorts of children who were not eligible to receive the vaccine (P=0.002 for testing for goodness of fit). Inclusion of the year as a factor improved the model (P=0.57 for testing for goodness of fit); this indicates that it was reasonable to assume that the secular changes observed in the nonvaccinated cohorts could be used to predict what would have happened without vaccination. The use of cases of disease from cohorts of children who were not eligible to receive the vaccine in order to predict disease trends in vaccine-eligible age groups can be justified because the program for infants is not expected to have any indirect (herd) effect.

The estimate of vaccine effectiveness is based on protection against all meningococcal group B strains. This is likely to be an underestimate of the true vaccine effectiveness because 4CMenB should not protect against all meningococcal group B strains. We attempted to estimate vaccine effectiveness against vaccine-preventable meningococcal group B strains by adjusting for the proportion of MATS-positive strains among the smaller number of culture-confirmed cases in the vaccine-eligible cohort. Our estimates also assumed that the proportion of strains that were MATS-positive would be similar in culture-confirmed and PCR-confirmed cases. In addition, we assumed no protection against MATS-negative strains, although there is likely to be some cross-protection, particularly in toddlers who will have received all three doses in the complete 4CMenB immunization schedule in the United Kingdom.[12] Finally, if 4CMenB protects only against these vaccine-preventable, MATS-positive meningococcal group B strains (although meningococcal group B disease would be less likely to develop in fully-immunized infants overall), then the smaller number of cases that do occur in immunized children would be more likely to be unpreventable by the vaccine (i.e., MATS-negative), although some cases of genuine vaccine failure will also occur. More accurate vaccine effectiveness against the vaccine-preventable strains may be possible with larger numbers of cases over time and improved nonculture methods of characterization of meningococci causing invasive disease.

In keeping with our previous report,[6] vaccine effectiveness among children who received a single priming dose in infancy was only 24.1% against all meningococcal group B strains, which is consistent with the lack of effect seen in infants who were 9 to 17 weeks of age. Vaccine effectiveness among infants who received two priming doses of 4CMenB was 52.7% — lower than previously reported.[6] This may be due to small numbers of cases in the earlier analysis and exclusion of the catch-up cohort from the current analysis. It could also be due to waning of protection within the first year of life, which may not have manifested in the previous analysis because of a shorter follow-up period.

The effectiveness of 4CMenB is also supported by data from a recent clinical trial,[13] a recent systematic review,[14] and other observational studies.[15-20] Although 4CMenB was licensed with a schedule of three priming doses in infants plus one booster dose, on the basis of limited data on immunogenicity, the United Kingdom implemented a reduced schedule for infants of two doses plus one booster dose.[21] This schedule has now been validated in a randomized, controlled trial that showed seroprotection in nearly all infants who received two priming doses.[13] In 2014, a mass immunization program was initiated in a region in Quebec, Canada, in response to a local outbreak of meningococcal group B disease; in that program, 82% of 59,000 persons who were 2 months to 20 years of age were immunized.[15] No cases of meningococcal group B disease occurred among vaccinees, and a multivariate analysis showed an estimated 78% reduction in meningococcal disease after the campaign. 4CMenB has also been administered to several thousand students during outbreaks in universities, and no additional cases have been identified.[16,18-20,22] As of December 2019, no major safety concerns had been identified after more than 3 million doses had been administered to infants,[23] older children and adolescents,[24,25] and premature infants.[26] Unlike the polysaccharide–protein conjugate vaccines, however, 4CMenB does not have any effect on menin-

gococcal group B carriage in immunized adolescents; therefore, immunization strategies with 4CMenB will need to focus on direct (individual) protection against meningococcal group B disease.[27]

In conclusion, 3 years after its implementation, 4CMenB continued to protect infants and toddlers against invasive meningococcal group B disease. This protection lasted for at least 2 years after receipt of two doses plus a booster dose.

Public Health England has legal permission, provided by Regulation 3 of the National Health Service ("Control of Patient Information") Regulations 2002, to process patient confidential information for national surveillance of communicable diseases. This includes responsibility of Public Health England to monitor the safety and effectiveness of vaccines, and individual patient consent is not required.

Supported by Public Health England.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the Public Health England health protection teams, child health record departments, and general practitioners for their help in ascertaining the vaccination status of the children, the scientific and administrative staff within the Public Health England Colindale Immunisation Department for clinical follow-up and data entry, and all laboratory staff at the Public Health England Meningococcal Reference Unit and the Public Health England Immunisation Team staff for their assistance with all work related to the enhanced surveillance of invasive meningococcal disease in England.

REFERENCES

1. Whittaker R, Dias JG, Ramliden M, et al. The epidemiology of invasive meningococcal disease in EU/EEA countries, 2004-2014. Vaccine 2017;35:2034-41.
2. Dretler AW, Rouphael NG, Stephens DS. Progress toward the global control of *Neisseria meningitidis*: 21st century vaccines, current guidelines, and challenges for future vaccine development. Hum Vaccin Immunother 2018;14(5):1146-60.
3. Tan LKK, Carlone GM, Borrow R. Advances in the development of vaccines against *Neisseria meningitidis*. N Engl J Med 2010;362:1511-20.
4. Donnelly J, Medini D, Boccadifuoco G, et al. Qualitative and quantitative assessment of meningococcal antigens to evaluate the potential strain coverage of protein-based vaccines. Proc Natl Acad Sci U S A 2010;107:19490-5.
5. Vogel U, Taha MK, Vazquez JA, et al. Predicted strain coverage of a meningococcal multicomponent vaccine (4CMenB) in Europe: a qualitative and quantitative assessment. Lancet Infect Dis 2013;13:416-25.
6. Parikh SR, Andrews NJ, Beebeejaun K, et al. Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in England: a national observational cohort study. Lancet 2016;388:2775-82.
7. Ladhani SN, Waight PA, Ribeiro S, Ramsay ME. Invasive meningococcal disease in England: assessing disease burden through linkage of multiple national data sources. BMC Infect Dis 2015;15:551.
8. Heinsbroek E, Ladhani S, Gray S, et al. Added value of PCR-testing for confirmation of invasive meningococcal disease in England. J Infect 2013;67:385-90.
9. Farrington CP. Estimation of vaccine effectiveness using the screening method. Int J Epidemiol 1993;22:742-6.
10. Snape MD, Saroey P, John TM, et al. Persistence of bactericidal antibodies following early infant vaccination with a serogroup B meningococcal vaccine and immunogenicity of a preschool booster dose. CMAJ 2013;185(15):E715-24.
11. Ladhani SN, Ramsay M, Borrow R, Riordan A, Watson JM, Pollard AJ. Enter B and W: two new meningococcal vaccine programmes launched. Arch Dis Child 2016;101:91-5.
12. Brunelli B, Del Tordello E, Palumbo E, et al. Influence of sequence variability on bactericidal activity sera induced by Factor H binding protein variant 1.1. Vaccine 2011;29:1072-81.
13. Martinón-Torres F, Safadi MAP, Martinez AC, et al. Reduced schedules of 4CMenB vaccine in infants and catch-up series in children: immunogenicity and safety results from a randomised open-label phase 3b trial. Vaccine 2017;35:3548-57.
14. Flacco ME, Manzoli L, Rosso A, et al. Immunogenicity and safety of the multicomponent meningococcal B vaccine (4CMenB) in children and adolescents: a systematic review and meta-analysis. Lancet Infect Dis 2018;18:461-72.
15. De Wals P, Deceuninck G, Lefebvre B, et al. Impact of an immunization campaign to control an increased incidence of serogroup B meningococcal disease in one region of Quebec, Canada. Clin Infect Dis 2017;64:1263-7.
16. McNamara LA, Shumate AM, Johnsen P, et al. First use of a serogroup B meningococcal vaccine in the US in response to a university outbreak. Pediatrics 2015;135:798-804.
17. Basta NE, Mahmoud AAF, Wolfson J, et al. Immunogenicity of a meningococcal B vaccine during a university outbreak. N Engl J Med 2016;375:220-8.
18. Duffy J, Johnsen P, Ferris M, et al. Safety of a meningococcal group B vaccine used in response to two university outbreaks. J Am Coll Health 2017;65:380-8.
19. Biswas HH, Han GS, Wendorf K, et al. Notes from the field: outbreak of serogroup B meningococcal disease at a university — California, 2016. MMWR Morb Mortal Wkly Rep 2016;65:520-1.
20. Thabuis A, Tararbit K, Taha MK, et al. Community outbreak of serogroup B invasive meningococcal disease in Beaujolais, France, February to June 2016: from alert to targeted vaccination. Euro Surveill 2018;23(28):1700590.
21. Findlow J, Borrow R, Snape MD, et al. Multicenter, open-label, randomized phase II controlled trial of an investigational recombinant meningococcal serogroup B vaccine with and without outer membrane vesicles, administered in infancy. Clin Infect Dis 2010;51:1127-37.
22. Basta NE, Mahmoud AAF, Borrow R. Meningococcal B vaccine during a university outbreak. N Engl J Med 2016;375:1595.
23. Bryan P, Seabroke S, Wong J, et al. Safety of multicomponent meningococcal group B vaccine (4CMenB) in routine infant immunisation in the UK: a prospective surveillance study. Lancet Child Adolesc Health 2018;2:395-403.
24. De Serres G, Billard MN, Gariépy MC, et al. Short-term safety of 4CMenB vaccine during a mass meningococcal B vaccination campaign in Quebec, Canada. Vaccine 2018;36:8039-46.
25. Mentzer D, Oberle D, Keller-Stanislawski B. Adverse events following immunisation with a meningococcal serogroup B vaccine: report from post-marketing surveillance, Germany, 2013 to 2016. Euro Surveill 2018;23(17):17-00468.
26. Kent A, Beebeejaun K, Braccio S, et al. Safety of meningococcal group B vaccination in hospitalised premature infants. Arch Dis Child Fetal Neonatal Ed 2019;104:F171-F175.
27. Marshall HS, McMillan M, Koehler AP, et al. Meningococcal B vaccine and meningococcal carriage in adolescents in Australia. N Engl J Med 2020;382:318-27.

Chapter Four

3. Invasive meningococcal disease in vulnerable populations

3.1. Study 6

Meningococcal B Vaccine Failure with a Penicillin-Resistant Strain in a Young Adult on Long-Term Eculizumab *Pediatrics* (2017)

Sydel R. Parikh, Jay Lucidarme, Coralie Bingham, Paul Warwicker, Tim Goodship, Ray Borrow, Shamez N. Ladhani

3.1.1. Study 6 Aim

This study aimed to describe a case of MenB disease due to a vaccine-preventable and penicillin-resistant strain in a fully immunized young adult on long-term complement inhibitor therapy and daily penicillin chemoprophylaxis. This paper was published with the aim of highlighting the difficulties in protecting patients on complement inhibitors against IMD.

3.1.2. Study 6 Summary

This case occurred in a 22-year old female who presented with very mild clinical presentations of fever, myalgia, sore throat and headache but no rash. Six months prior to this she was diagnosed with atypical haemolytic uremic syndrome (aHUS). She was placed on Eculizumab, which is a humanized monoclonal antibody that is a terminal complement inhibitor used as treatment for aHUS among other conditions. She had received group C meningococcal vaccine as part of the national programme in 2000 as well as the MenACWY vaccine. She received two doses of 4CMenB 1 month apart, following her aHUS diagnosis. It is difficult to interpret antibody titers for patients on eculizumab therapy as the drug inactivates the assay which uses exogenous human complement. The case was also on long-term penicillin prophylaxis for protection against IMD.

The infecting strain was shown to be fully preventable by the 4CMenB vaccine and was MATS positive on one antigen (NHBA). The minimum inhibitory concentration for the infecting strain was 0.5 mg/L for penicillin, which was double the threshold (0.25 mg/L) for penicillin resistance. Genomic analysis revealed the *penA* allele contained 3 mutations associated with reduced penicillin sensitivity. Further comparisons within the PubMLST *Neisseria* database suggested a recombination event in an ancestral strain involving a putative gonococcal origin, a species associated with high rates of antibiotic resistance.

3.1.3. Study 6 New knowledge gained

This was the first case of 4CMenB vaccine failure on a patient receiving long-term eculizumab for aHUS. Although antibiotic resistance is very rare among meningococci (<5%) the case was infected with a strain with a high resistance to the antibiotic chemoprophylaxis she was on. This study served to highlight the importance of raising awareness of meningococcal disease in patients on eculizumab therapy, even when they are fully vaccinated and complying with prophylactic prescriptions.

3.2. Study 7

Primary meningococcal conjunctivitis: Summary of evidence for the clinical and public health management of cases and close contacts *Journal of Infection* (2019)
Sydel R. Parikh, Helen Campbell, Sema Mandal, Mary E. Ramsay, Shamez N. Ladhani

3.2.1. Study 7 Aim

This study aimed to compile a review of the literature in order to provide robust evidence base to support recommendations for clinical and public health management of primary meningococcal conjunctivitis (PMC) cases and their close contacts.

3.2.2. Study 7 Summary

A literature review was performed by searchin PubMed with the terms “Meningococcal”, “Conjunctivitis”, “primary meningococcal conjunctivitis” and any combination of “transmission” or “invasive disease”. Publication dates and languages were not limited. Ovid MEDLINE was searched via PubMed, EMBASE and NHS evidence (up to December 2018 week 3). The advanced search mode was used including the terms “Meningococcal”, “Conjunctivitis”, “primary meningococcal conjunctivitis” and any combination of “transmission” or “invasive disease” or “contacts” or “management” or “treatment”. Publication dates and languages were not limited. Case series and review articles that summarised previous publications on PMC were prioritized; the individual publications cited in such studies were not retrieved for additional review.

Findings were summarised and sorted under three categories (with some articles in more than one category):

1. Reports of IMD in patients with PMC
2. Reports of IMD in close contacts of patients with PMC
3. Reports of identical strains from PMC cases and screening of their household or close contacts in the absence of invasive disease

3.2.3. Study 7 Results

This study provided a clear report of the published data on PMC as it pertains to clinical and public health management of PMC cases and their close contacts. In the UK there is currently no consensus on this management. This review identified a 10-29% risk of IMD among PMC cases where systemic symptoms typically occur within two days (range: 3 hours to 4 days) (Reese, 1936; Odegaard, 1983; Barquet et al., 1990; Ellis et al., 1992; Stansfield et al., 1994). The review also highlighted that systemic antibiotic therapy for PMC was more effective than topical antibiotic therapy alone in the prevention of systemic disease (Newton and Wilson, 1977; Odegaard, 1983; Barquet et al., 1990). One study showed the risk of developing IMD was 19 times greater when cases were treated with topical antibiotics alone than if combined with systemic antibiotic treatment (Barquet et al., 1990).

In light of these findings on the recommendation for antibiotic treatment of PMC cases this review raised three important questions and used the findings of the review to answer them as they pertain to the clinical and public health management of these cases:

1. Unless a Gram stain of the conjunctival swab is performed quickly, the culture results of the bacterial eye swab may take at least 48 h to be reported. Therefore, should PMC cases initially treated with topical antibiotics alone be recalled for systemic antibiotics?
2. Can children with PMC be treated with oral antibiotics when *N. meningitidis* is confirmed as the cause of the conjunctivitis?
3. What is the duration of oral antibiotic treatment in an otherwise well child with PMC and no systemic symptoms?

3.2.4. Study 7 New knowledge gained

This study provided a clear report of the published data on PMC as it pertained to clinical and public health management of PMC cases and their close contacts. These findings provided support for current guidelines on the public health management of PMC cases in England and served to highlight the need for clearer, more up to date clinical recommendations for the treatment of PMC cases, in so much as to prevent progression to systemic disease.

3.3. Study 8

Lower risk of invasive meningococcal disease during pregnancy; national prospective surveillance in England, 2011-2014 ***British Journal of Obstetrics and Gynaecology*** **(2019)**

SR Parikh, R Borrow, ME Ramsay, SN Ladhani

3.3.1. Study 8 Aim

The objective of this study was to estimate the risk of IMD in pregnant women compared with non-pregnant women and to describe the epidemiology, clinical characteristics and outcomes of IMD in pregnant women in England over a 4 year period.

3.3.2. Study 8 Summary

Enhanced national surveillance data was used in conjunction with short clinical questionnaires completed by general practitioners for laboratory confirmed cases of IMD in England since 01 January 2011. All laboratory confirmed cases of IMD in women of reproductive age (15-44 years) in England from 01 January 2011 to 31 December 2014 (4 years) were included. Women in this cohort may have been eligible to receive the MenC conjugate vaccine but neither the 4CMenB nor the MenACWY vaccine were part of the national immunisation programme during this period.

Information collected included comorbidities, clinical presentation, intensive care admission, and outcomes. Incomplete or missing information in the questionnaires was followed up by telephoning the GP, contacting the patient's hospital clinician, or requesting additional information from the local PHE health protection team (HPT). If needed, additional information was sought from HPZone, and from the electronic death registration records from the Office for National Statistics (ONS).

For fatal cases, the date of death was confirmed using the Personal Demographics Service (PDS). Online annual reports of the Confidential Enquiry into Maternal Deaths (CEMD, www.npeu.ox.ac.uk/mbrrace-uk/reports/confidential-enquiry- into-maternal-deaths) were also accessed to identify any pregnancy-related deaths resulting from IMD during the surveillance period. The HPZone records for neonatal IMD cases confirmed during the surveillance period were checked for any mention of maternal illness during the perinatal period.

General population and maternity data (including total conceptions) for England was obtained from ONS. These were used for denominator populations (ONS Population Estimates Tool, accessed 02 May 2019; ONS Conception Statistics; accessed 02 May 2019).

Pregnant years were estimated as the product of the total number of conceptions between 2011 and 2014 and the maximum possible gestation period (9 months). This was then used to estimate non-pregnant years as the difference between the total female population aged 15–44 years and pregnant years.

Demographic, clinical questionnaire and microbiological data were entered into a single Microsoft Access Database cleaned and de-duplicated before being imported into STATA 13.0 for analysis. Descriptive statistics were given for demographics and clinical characteristics of pregnant women with IMD. Core outcomes and estimates of IMD incidence rates with Poisson 95% confidence intervals for pregnant and non-pregnant women along with incidence rate ratios pregnant and non-pregnant women were also performed.

3.3.3. Study 8 Results

Between 2011 and 2014 (317,417,121 woman-years) there were 2980 cases of IMD in England. Clinical information was available for all 2980 cases. Of these, 1502 occurred in females across England over the four-year study period, 310 (20.6%) of which occurred in women of reproductive age (median age 20 years; Q1, 18 year; Q3, 28.5 years). Among those of reproductive age, four women were reported pregnant at the time of IMD confirmation (1.3%). The four cases in otherwise healthy pregnant women were confirmed across all trimesters and all survived; one case in the first trimester had a septic miscarriage. The incidence of IMD was lower in pregnant than in non-pregnant women (0.16 compared with 0.76 per 100,000 pregnant and non-pregnant years, respectively), giving a lower risk of IMD in pregnant women (IRR, 0.21; CI 0.06–0.54).

3.3.4. Study 8 New knowledge gained

This study was the first to assess the risk of IMD in pregnancy and established that in our study population, pregnant women were nearly five times less likely to develop IMD compared to non-pregnant women, although the infection could still be severe. This knowledge could be used to alleviate worries among pregnant women and could also be used as supporting evidence for vaginal swabbing prior to delivery.

Published papers presented in Chapter Four

Study 6: Meningococcal B Vaccine Failure with a Penicillin-Resistant Strain in a Young Adult on Long-Term Eculizumab *Pediatrics* (2017)

Meningococcal B Vaccine Failure With a Penicillin-Resistant Strain in a Young Adult on Long-Term Eculizumab

Sydel R. Parikh, MSc,[a] Jay Lucidarme, PhD,[b] Coralie Bingham, MD,[c] Paul Warwicker, MD,[d] Tim Goodship, MD,[e] Ray Borrow, PhD,[b] Shamez N. Ladhani, MD[a,f]

abstract

We describe a case of invasive meningococcal disease due to a vaccine-preventable and penicillin-resistant strain in a fully immunized young adult on long-term complement inhibitor therapy and daily penicillin chemoprophylaxis. Eculizumab is a humanized monoclonal antibody that binds human complement C5 protein and inhibits the terminal complement pathway. It is currently recommended for the treatment of complement-mediated thrombotic microangiopathies. An unwanted complication of inhibiting complement, however, is an increased risk of invasive meningococcal disease. Here, we report the first case of meningococcal group B vaccine failure in a young adult receiving eculizumab for atypical hemolytic uremic syndrome. She developed invasive meningococcal disease due to a vaccine-preventable and penicillin-resistant meningococcal group B strain 4 months after receiving 2 doses of meningococcal group B vaccine while on oral penicillin prophylaxis against meningococcal infection.

Monoclonal antibodies are increasingly used to treat a range of medical conditions. Eculizumab (Soliris; Alexion, New Haven, CT) is a humanized monoclonal antibody that is a terminal complement inhibitor used to treat paroxysmal nocturnal hemoglobinuria,[1] and atypical hemolytic uremic syndrome (aHUS),[2] although its use is extending to treat other immune-mediated conditions.[3–5] In aHUS, uncontrolled complement activation due to defects of complement regulation leads to platelet, leukocyte, and endothelial cell activation and thrombotic microangiopathy.[2]

Eculizumab binds with high affinity to human C5 complement and blocks the generation of complements C5a and C5b-9. This prevents the formation of membrane attack complexes and proinflammatory pathway activation, thus preventing end-organ damage.[1]

An unwanted complication of complement inhibition, however, is an increased risk of infection with encapsulated bacteria, especially *Neisseria meningitidis*.[6] Consequently, patients on eculizumab are advised to receive meningococcal vaccination at least 14 days before initiating treatment.[7]

Until recently, licensed meningococcal vaccines protected against only 4 of the 12 known meningococcal serogroups (A, C, W, and Y). In Europe, serogroup B (MenB) is responsible for nearly all invasive meningococcal disease (IMD) cases.[8] In 2013, a multicomponent, protein-based, broad-spectrum meningococcal vaccine (4CMenB, Bexsero; GSK Biologicals, Siena, Italy) was licensed for protection against MenB, although the vaccine antigens can be found on the surface of all meningococci and, therefore, offer

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Mr Parikh and Dr Ladhani are responsible for national surveillance of meningococcal disease in England through the Immunisation Department at Public Health England, and drafted the initial manuscript; Drs Borrow and Lucidarme are responsible for providing a national reference laboratory service for meningococcal disease through the meningococcal reference unit at Public Health England; they carried out the molecular and genomic analysis of the meningococcal isolate, contributed to the discussion, and reviewed and revised the manuscript; Drs Bingham, Warwicker, and Goodship are clinicians who manage patients with complex renal diseases, including those receiving complement inhibitors; they contributed to the discussion, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: https://doi.org/10.1542/peds.2016-2452

Accepted for publication Feb 3, 2017

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

To cite: Parikh SR, Lucidarme J, Bingham C, et al. Meningococcal B Vaccine Failure With a Penicillin-Resistant Strain in a Young Adult on Long-Term Eculizumab. *Pediatrics*. 2017;140(3):e20162452

protection regardless of capsular group. In the United Kingdom, the quadrivalent ACWY meningococcal conjugate vaccine (MenACWY) and 4CMenB are recommended for at-risk individuals, including those receiving complement inhibitors.[9] Here, we report the first case of 4CMenB vaccine failure in a fully immunized young adult on penicillin prophylaxis who developed IMD caused by a vaccine-preventable and penicillin-resistant MenB strain during treatment with eculizumab for aHUS.

CASE DESCRIPTION

A 22-year-old woman presented to the emergency department with fever, myalgia, lethargy, sore throat, and headache, but no rash, photophobia, or neck stiffness. Six months previously, she was diagnosed with aHUS associated with the *CFH* mutation c.3643C>G; p.Arg1215Gly identified through genetic testing,[10] after presenting with vomiting and diarrhea, headache, oliguria, hemolytic anemia, severe thrombocytopenia with bruising, acute renal injury requiring dialysis, and raised lactate dehydrogenase, consistent with a thrombotic microangiopathy. At the time, she was started on long-term eculizumab and penicillin prophylaxis. She had no other significant medical history.

Clinical examination was unremarkable. Her blood counts revealed elevated white cell (17.0×10^9/L) and neutrophil (15.8×10^9/L) counts, with normal renal and liver function. The C-reactive protein was 5 mg/L initially but increased to 150 mg/L within 20 hours before falling gradually. Lumbar puncture revealed no evidence of meningitis. She was treated with intravenous ceftriaxone (2 g twice daily) for 7 days followed by 10 days of oral ciprofloxacin 500 mg twice daily. Gram-negative diplococci were identified in the blood culture after 24 hours. She was discharged within 24 hours and has remained well on oral penicillin prophylaxis.

VACCINATION HISTORY

She had received the group C meningococcal conjugate vaccine as part of the national program in 2000 and the MenACWY vaccine with 2 doses of 4CMenB given 1 month apart when she was diagnosed with aHUS. Two months after MenACWY vaccination, serum bactericidal antibody titers using rabbit complement were 1024, 8192, 1024, and 512 for serogroups A, C, W, and Y, respectively. MenB serum bactericidal antibody titers for patients on eculizumab therapy are difficult to interpret because this assay uses exogenous human complement, which is inactivated by eculizumab.

MICROBIOLOGY

The meningococcal blood culture isolate was sent to the national reference laboratory and confirmed as nonserogroupable with a minimum inhibitory concentration of 0.5 mg/L for penicillin, which was double the threshold (0.25 mg/L) for penicillin resistance. Genomic analysis identified the isolate as belonging to the ST-162 clonal complex, a strain with established pathogenic potential. The capsular gene *csb* (siaDb), however, was interrupted by an IS*1301*-related sequence, making the isolate unlikely to cause disease in immunocompetent individuals. Its *penA* allele (*neis1753* allele 23) contained 3 mutations associated with reduced penicillin sensitivity (F504L, A510V, I515V). Within the PubMLST *Neisseria* database (pubmlst.org/neisseria; accessed August 12, 2015), this allele was predominantly associated with *Neisseria gonorrhoeae* (82/1758 annotated genomes versus 2/5464 annotated meningococcal genomes). The allele was not observed among any annotated genomes for *Neisseria lactamica* (n = 127), *Neisseria subflava* (n = 20), *Neisseria polysaccharea* (n = 15), *Neisseria mucosa* (n = 14), or other *Neisseria* species. Comparison of the broader genomic region (*neis1740* to *neis1773*) with other cc162 genomes by using the PubMLST genome comparator tool revealed an uncharacteristic region spanning from *neis1750* to *neis1756*. As with *neis1753*, the *neis1754*, *neis1755*, and *neis1756* alleles were highly associated with *N gonorrhoeae*, whereas *neis1750* and *neis1751* were novel variants. This suggested a recombination event in an ancestral strain involving DNA of putative gonococcal origin.

The isolate also possessed genes for PorA P1.22,14, factor H binding protein peptide 3.31, and neisserial heparin binding antigen peptide 20, and was Neisserial adhesion A (*nadA*) negative. Meningococcal Antigen Typing System analysis confirmed the strain as vaccine-preventable because of neisserial heparin binding antigen positivity.

DISCUSSION

This case highlights the difficulties in protecting patients on complement inhibitors against meningococcal disease, even with vaccination and antibiotic chemoprophylaxis. Individuals on long-term eculizumab who are not otherwise immunosuppressed can produce high serum bactericidal antibody titers after meningococcal vaccination. However, the critical functions of the terminal complement pathway and, therefore, the ability to attract proinflammatory cells and initiate cell destruction by triggering pore formation, are impaired (even though the proximal complement pathway remains intact). Inherited

deficiencies of the terminal complement pathway are rare (0.03% of the general population), but associated with a 7000 to 10 000-fold higher risk of IMD, with 50% to 60% experiencing ≥1 IMD episode.[11] In those with C5 deficiency, meningococci are responsible for >95% of invasive infections, with meningitis being the most common presentation (77%), and 42% suffer from recurrent disease, both in terms of relapse and newly acquired infections.[11] Recurrent infections occur despite an adequate antibody response against the infecting isolates; in vitro studies have shown that these antibodies will kill the homologous isolate, but only when complement is added to the assay.[12]

Interestingly, individuals with complement deficiency often have mild disease with low case fatality.[11] One possible explanation is a less intense inflammatory response to infection because of lower endotoxin release from the bacterial surface in the absence of an intact terminal complement pathway.[11] We have recently shown that eculizumab inhibited complement-mediated serum bactericidal activity but did not impede opsonophagocytic activity in patients on long-term eculizumab therapy.[13] Opsonophagocytic activity is triggered by binding of C3 complement without requirement of the terminal complement and may, therefore, help protect against severe infection.

The increased risk of IMD in patients receiving eculizumab is well-recognized,[7] with clear recommendations for meningococcal vaccination of patients at least 2 weeks before commencing treatment.[14] Many clinicians additionally advocate lifelong antibiotic chemoprophylaxis for added protection because of the continued high risk of IMD despite adequate postvaccination antibody responses.[15–17] In a recent evaluation of 195 patients on eculizumab, 2 IMD cases were identified during 467 patient-years of eculizumab exposure (0.42 infections/100 patient-years).[18] Both had received various meningococcal vaccines, but developed IMD due to a nonvaccine serogroup. In another report, a 19-year-old with known factor H mutation, 3 renal transplants, and receiving several immunosuppressives in addition to eculizumab developed meningococcal group W (MenW) septicemia.[16] She had been immunized 18 months previously with a MenACWY polysaccharide vaccine, which is likely to be less protective than the equivalent conjugate vaccine.

Recently, a toddler with aHUS diagnosed in infancy and receiving long-term eculizumab developed MenW septicemia despite previous immunization with the MenACWY conjugate vaccine.[15] He was also on amoxicillin prophylaxis at the time, and the responsible MenW strain had intermediate penicillin sensitivity, with a minimal inhibitory concentration of 0.13 mg/L (sensitive 0.06 mg/L, resistant >0.25 mg/L). This child, too, had mild disease without complications. After her illness, she had nonprotective antibody titers against serogroups C, W, and Y, but responded with high antibody titers after a further dose of the MenACWY conjugate vaccine.

The recent licensure of 4CMenB was heralded as a major breakthrough in the global fight against meningococcal disease because it aimed to provide broad protection against all capsular groups. Our patient had been immunized with the MenACWY conjugate vaccine and 4CMenB, and was on long-term penicillin prophylaxis when she developed MenB disease due to a penicillin-resistant and vaccine-preventable strain. Current guidelines recommend testing antibody responses in patients receiving eculizumab before and 4 to 6 weeks after meningococcal vaccination, and subsequently every 1 to 3 years with a view to reimmunize if antibody titers are below protective thresholds.[18,19] More data are needed to support this recommendation, given that antibodies require a functional terminal complement pathway to kill the meningococci efficiently. The development of IMD due to a penicillin-resistant strain in our patient and the published pediatric case is also concerning, given that penicillin resistance is rare (<5%) among invasive meningococci. These 2 cases highlight the importance of raising awareness of meningococcal disease, including use of information cards to be carried by patients and their caregivers, and to seek medical attention early.[20] The development and maintenance of national specialized centers will play a vital role in monitoring the risks and outcomes of adverse events, including IMD, in children and adults on long-term eculizumab.[20,21]

ABBREVIATIONS

aHUS: atypical hemolytic uremic syndrome
IMD: invasive meningococcal disease
MenACWY: quadrivalent ACWY meningococcal conjugate vaccine
MenB: meningococcal group B
MenW: meningococcal group W
4CMenB: multicomponent, protein-based, broad-spectrum meningococcal vaccine

FINANCIAL DISCLOSURE: Drs Borrow, Goodship, and Warwicker have performed contract research for Alexion on behalf of their respective institutions, unrelated to this current study, and received no personal remuneration for their work; the other authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. Hillmen P, Young NS, Schubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 2006;355(12):1233–1243
2. Legendre CM, Licht C, Muus P, et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. *N Engl J Med*. 2013;368(23):2169–2181
3. Reis ES, Mastellos DC, Yancopoulou D, Risitano AM, Ricklin D, Lambris JD. Applying complement therapeutics to rare diseases. *Clin Immunol*. 2015;161(2):225–240
4. Nester CM, Brophy PD. Eculizumab in the treatment of atypical haemolytic uraemic syndrome and other complement-mediated renal diseases. *Curr Opin Pediatr*. 2013;25(2):225–231
5. Bomback AS. Eculizumab in the treatment of membranoproliferative glomerulonephritis. *Nephron Clin Pract*. 2014;128(3-4):270–276
6. Nester CM, Thomas CP. Atypical hemolytic uremic syndrome: what is it, how is it diagnosed, and how is it treated? *Hematology Am Soc Hematol Educ Program*. 2012;2012:617–625
7. US Food and Drug Administration. Solaris (Eculizumab) postmarket drug safety information for patients and providers. Available at: https://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM217725.pdf. Accessed June 16, 2017
8. Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. *Vaccine*. 2009;27(suppl 2):B51–B63
9. Public Health England. Meningococcal: the green book, chapter 22. Available at: https://www.gov.uk/government/publications/meningococcal-the-green-book-chapter-22. Accessed June 16, 2017
10. Warwicker P, Goodship TH, Donne RL, et al. Genetic studies into inherited and sporadic hemolytic uremic syndrome. *Kidney Int*. 1998;53(4):836–844
11. Figueroa JE, Densen P. Infectious diseases associated with complement deficiencies. *Clin Microbiol Rev*. 1991;4(3):359–395
12. Figueroa J, Andreoni J, Densen P. Complement deficiency states and meningococcal disease. *Immunol Res*. 1993;12(3):295–311
13. Findlow J, Bai X, Carr D, et al. *Effect of the Eculizumab (Solaris), on the Meningococcal Serogroup B Serum Bactericidal Antibody Activity and Opsonophagocytic Activity*. Amsterdam, The Netherlands: Congress of EMGM; 2015
14. Keating GM. Eculizumab: a review of its use in atypical haemolytic uraemic syndrome. *Drugs*. 2013;73(18):2053–2066
15. Cullinan N, Gorman KM, Riordan M, Waldron M, Goodship TH, Awan A. Case report: benefits and challenges of long-term eculizumab in atypical hemolytic uremic syndrome. *Pediatrics*. 2015;135(6). Available at: www.pediatrics.org/cgi/content/full/135/6/e1506
16. Struijk GH, Bouts AH, Rijkers GT, Kuin EA, ten Berge IJ, Bemelman FJ. Meningococcal sepsis complicating eculizumab treatment despite prior vaccination. *Am J Transplant*. 2013;13(3):819–820
17. Zlamy M, Hofer J, Elias J, et al. Immunogenicity of meningococcus C vaccination in a patient with atypical hemolytic uremic syndrome (aHUS) on eculizumab therapy. *Pediatr Transplant*. 2012;16(6):E246–E250
18. Hillmen P, Muus P, Röth A, et al. Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria. *Br J Haematol*. 2013;162(1):62–73
19. Group aRD. Atypical haemolytic uraemic syndrome (aHUS) – clinician information. Available at: http://rarerenal.org/clinician-information/haemolytic-uraemic-syndrome-atypical-ahus-clinician-information/. Accessed January 18, 2016
20. Loirat C, Fakhouri F, Ariceta G, et al; HUS International. An international consensus approach to the management of atypical hemolytic uremic syndrome in children. *Pediatr Nephrol*. 2016;31(1):15–39
21. Sheerin NS, Kavanagh D, Goodship TH, Johnson S. A national specialized service in England for atypical haemolytic uraemic syndrome—the first year's experience. *QJM*. 2016;109(1):27–33

Study 7: Primary meningococcal conjunctivitis: Summary of evidence for the clinical and public health management of cases and close contacts *Journal of Infection* (2019)

Journal of Infection 79 (2019) 490–494

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Primary meningococcal conjunctivitis: Summary of evidence for the clinical and public health management of cases and close contacts

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ARTICLE INFO

Article history:
Accepted 20 October 2019
Available online 25 October 2019

Keywords:
Primary meningococcal conjunctivitis
Chemoprophylaxis
Invasive meningococcal disease

SUMMARY

Background: *Neisseria meningitidis* is a rare cause of acute bacterial conjunctivitis but can progress to invasive meningococcal disease (IMD) in the case and their close contacts. There is, however, a lack of consensus on the clinical and public health management of primary meningococcal conjunctivitis (PMC).
Methods: We searched Ovid MEDLINE via PubMed, EMBASE and NHS evidence (up to June 2019) for all publications relating to meningococcal conjunctivitis to provide an evidence-base for developing guidelines for the management of PMC cases and their close contacts.
Results: The review identified a 10–29% risk of IMD among PMC cases within two days of onset of eye infection (range: 3 h to 4 days). In one study, the risk of IMD in PMC cases treated with systemic antibiotics was 19 times lower than topical antibiotics alone ($p = 0.001$). IMD among close contacts of PMC cases is uncommon but potentially fatal. Whether meningococcal vaccination for PMC cases or close contacts provides any additional benefit is unclear.
Conclusions: Systemic antibiotic treatment significantly reduces the risk of invasive disease in PMC cases, while antibiotic chemoprophylaxis for close contacts will reduce their risk of secondary IMD. These findings need to be highlighted in relevant clinical and public health guidelines.

Key points

In patients with primary meningococcal conjunctivitis, systemic antibiotic treatment significantly reduces the risk of invasive meningococcal disease compared to topical antibiotics alone, while antibiotic chemoprophylaxis for close contacts reduces their risk of developing secondary invasive disease.

Introduction

Neisseria meningitidis is a Gram-negative diplococcus that frequently colonises the upper respiratory tract of adolescents and young adults. Rarely, the pathogen will cause serious invasive infection, including meningitis and septicaemia, which are both associated with high morbidity and mortality. Acute conjunctivitis is the most common disorder of the eye, especially in children. In neonates, *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are the main causes of ophthalmia neonatorum, while *Haemophilus influenzae, Streptococcus pneumoniae* and adenoviruses are the most important pathogens in older infants; *Staphylococcus aureus* is a common cause at any age. Bacterial conjunctivitis is rarely caused by *N. meningitidis*, although the true incidence is most likely underestimated because most cases of conjunctivitis are treated empirically, without adequate microbiological investigations, and recover without complications.[1]

Primary meningococcal conjunctivitis (PMC) refers to infection of the conjunctiva, which may or may not progress to systemic disease, while secondary meningococcal conjunctivitis is an unusual complication of systemic meningococcal disease. PMC occurs after direct inoculation of the meningococcus into the conjunctival sac through direct contact or the airborne route. In neonates, this is often acquired vertically from the mother's genitourinary tract.[2] Most cases of PMC recover with appropriate treatment, although complications such as corneal ulcers, keratitis, sub-conjunctival

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https://doi.org/10.1016/j.jinf.2019.10.015

hemorrhage and iritis have been reported.[3] Some studies have suggested PMC to be responsible for around 2% of all bacterial conjunctivitis, but larger studies have estimated the incidence to be well below 1%.[4–6]

There is currently no consensus on the management of individuals with PMC or their close contacts. In the United Kingdom and Australia for example, guidelines for the public health management of meningococcal disease state that PMC cases are at an increased risk of developing invasive meningococcal disease (IMD),[7,8] while US guidance attributes no additional risk of IMD to PMC cases.[9] At the same time, neither the UK National Institute for Health and Care Excellence (NICE) clinical guidelines for Bacterial Meningitis and Meningococcal Septicaemia, which aims to reduce deaths and disability by promoting early recognition of symptoms and timely effective management, nor the UK's College of Optometrists' clinical guidelines for Bacterial Conjunctivitis[10] mentions meningococcal conjunctivitis as a potential precursor of IMD.[11] Similarly, the British National Formulary (BNF), which provides best practice guidance on the drug treatment of medical conditions does not provide any specific recommendations for the treatment PMC in its "Antibacterials for eye infections" section.[12]

In addition to the clinical management of PMC cases, there is also a lack of consensus on the public health management of close contacts of PMC cases. Again, both the UK[13] and Australian[8] public health management guidelines state that close contacts of PMC cases are at an increased risk of IMD and, therefore, recommend antibiotic chemoprophylaxis for them in order to prevent secondary IMD, whereas the US guidance does not acknowledge any increased risk and, therefore, does not make any recommendations for antibiotic chemoprophylaxis for close contacts.[9] There are also conflicting recommendations for meningococcal vaccination; the UK guidelines recommend no vaccination for PMC cases or their close contacts, while the Australian guidelines recommend meningococcal vaccination if the responsible strain belongs to serogroups A, C, W or Y.[13,14] Clinical and public health guidelines for meningococcal disease from most other countries do not make any specific recommendations for PMC cases or their close contacts.[14] We, therefore, performed a review of the literature in order to provide a robust evidence base to support recommendations for clinical and public health management of PMC cases and their close contacts.

Methods

We searched PubMed with the terms "Meningococcal", "Conjunctivitis", "primary meningococcal conjunctivitis" and any combination of "transmission" or "invasive disease". Publication dates and languages were not limited. We searched Ovid MEDLINE via PubMed, EMBASE and NHS evidence (up to December 2018 week 3). The advanced search mode was used including the terms "Meningococcal", "Conjunctivitis", "primary meningococcal conjunctivitis" and any combination of "transmission" or "invasive disease" or "contacts" or "management" or "treatment". Publication dates and languages were not limited. Case series and review articles that summarised previous publications on PMC were prioritised; the individual publications cited in such studies were not retrieved for additional review.

Results

Primary Meningococcal Conjunctivitis

PMC may present as acute or hyperacute purulent conjunctivitis which is clinically indistinguishable from conjunctivitis caused by *N.gonorrhoeae*.[15] Published studies have reported 10–29% of PMC cases may lead to IMD (Table 1), with systemic symptoms occurring within two days of onset of eye infection (*range*: 3 h to 4 days).[3,16–19] Systemic antibiotic therapy for PMC is more effective than topical antibiotic therapy alone in prevention of systemic disease.[3,15–17,20–26] In one study, the risk of developing IMD when PMC cases were treated with topical antibiotics alone was 19 times greater ($p = 0.001$) than if combined with systemic antibiotic treatment.[3]

Antibiotic chemoprophylaxis for close contacts

Patients with PMC may also transmit the meningococcus to close contacts, who may then go on to develop systemic disease. In several studies, screening of household and close contacts of PMC cases found them to be carrying identical strains to the one responsible for the conjunctivitis.[27–29] This suggests that meningococcal strains causing PMC can circulate among the household and close contacts, potentially putting them at risk of invasive disease. This risk, however, has not been quantified and there are very few such instances reported in the literature,[16,30] although at least three deaths from IMD following close contact with a case of PMC have been reported.[16,17,30]

Discussion and clinical implications

Neisseria meningitidis is a rare cause of acute bacterial conjunctivitis in any age group but it is important to identify this pathogen as the cause because of an increased risk of invasive meningococcal disease among both the PMC cases themselves and their close contacts.[31] It is also important to distinguish between meningococcal and gonococcal infection when Gram-negative diplococci are identified on microscopy or culture of an eye swab. This is because treatment, contact tracing and outcomes are different for the two aetiologies. Reassuringly, empiric treatment for gonococcal conjunctivitis already includes systemic antibiotics,[31] which will also treat PMC. Based on the current literature, patients with PMC should be treated as early as possible with systemic antibiotics in addition to topical antibiotics to reduce the risk of developing IMD. Antibiotic chemoprophylaxis should also be offered to household and close contacts of PMC cases because of a small, unquantified but potentially fatal risk of IMD.

The recommendation to treat PMC cases with systemic antibiotics in addition to topical antibiotics raises three important questions:

(i) *Unless a Gram stain of the conjunctival swab is performed quickly, the culture results of the bacterial eye swab may take at least 48 h to be reported. Therefore, should PMC cases initially treated with topical antibiotics alone be recalled for systemic antibiotics?*

Among the published cases, Gram-negative diplococci were usually identified on a Gram stain performed on the initial conjunctival swab and, therefore, systemic antibiotics were initiated relatively quickly. However, given the continuing risk of invasive disease up to 4 days after onset of conjunctivitis, it would be prudent to initiate systemic antibiotics as soon as PMC is diagnosed, even if the patient is systemically well.

(ii) *Can children with PMC be treated with oral antibiotics when N. meningitidis is confirmed as the cause of the conjunctivitis?*

Both intravenous[3,16,17] and oral[15,30] antibiotics have been used successfully to treat PMC cases and prevent progression to systemic disease, suggesting that a treatment course of oral antibiotics should be adequate in otherwise well children with PMC alone and no systemic symptoms. In neonates with conjunctivitis, it may be prudent to initiate treatment with an intravenous cephalosporin

Table 1
Summary of publications relating to primary meningococcal conjunctivitis (PMC).

Reports of invasive meningococcal disease (IMD) in patients with primary meningococcal conjunctivitis (PMC)			
Citation (country)	Ref No.	Study type	Key results
Barquet et al., 1990 (Spain)	3	Observational cohort and literature review	*N. meningitidis* found in 2.0% (21/1030) of all acute bacterial conjunctivitis seen in the hospital over 5 years. Six of the 21 (28.6%) PMC cases resulted in systemic disease 63 PMC cases identified in the literature, including 9 (14.3%) reported with systemic disease Among PMC cases with systemic disease ($n=15$), 2 died (overall CFR, 13.3%) Risk of IMD among PMC cases was 19 times greater among those who received topical antibiotics alone (31.7%) compared to those who received systemic antibiotic therapy (2.38%); $p=0.001$
Moraga Llop et al., 1996 (Spain)	21	Prospective observational study	34 PMC cases identified over a 10-year period in a single hospital (mean age, 3.5 years) and 10 (29.4%) developed IMD. PMC was bilateral in 7 patients and unilateral in 27 Topical antibiotics only were given to 24 patients and 10 (41.7%) developed IMD compared to none of the 10 who received systemic antibiotics ($p=0.04$) None of the patients died and none developed ocular sequelae.
Stansfield et al., 1994 (Scotland)	17	Case series	8/53 (15.1%) PMC cases had either concurrent or subsequent IMD. Detailed account of 3/8 PMC cases reported - two were associated with systemic sepsis and one died
Ellis et al., 1992 (UK)	18	Case series	2 cases of perinatally-acquired PMC in neonates which rapidly progressed to IMD at 60 h and 72 h of age, respectively. Both neonates were initially treated with neomycin eye ointment only
Mangiaracine and Pollen, 1944 (USA)	26	Case series	3/10 (30%) PMC cases (age range: 14 weeks to 15 years) went on to develop IMD; all 3 were initially only treated with topical solutions/antibiotics.
Odegaard et al., 1983 (Norway)	16	Case report	Single case in 15-year-old male that progressed to IMD with a fatal outcome; initially treated with only chloramphenicol eye drops; 18 h after the eye swab was taken, meningococcal serogroup B was isolated. Topical antibiotic therapy was not changed to systemic antibiotics
Nussbaum et al., 1978 (USA)	23	Case report	Single case of PMC progressing to IMD in an infant, who was initially treated with ophthalmic solution alone.
Dillman, 1967 (USA)	22	Case report	Single case of PMC that progressed to IMD in a 24-year old male who was initially treated with sulfacetamide ointment only
Reese, 1936 (USA)	19	Case report	Single case of unilateral PMC that progressed to IMD in a nurse who had been on duty with a case from an IMD outbreak
Reports of invasive meningococcal disease (IMD) in close contacts of patients with primary meningococcal conjunctivitis (PMC)			
Citation	Ref No.	Study type	Key results
Stansfield et al., 1994 (Scotland)	17	*Case series*	3 PMC cases associated with systemic sepsis reported A 10-year-old boy with bilateral conjunctivitis was prescribed topical chloramphenicol and discharged home; eye swab culture subsequently grew N. meningitidis (C:2b:P1.2), while led to immediate systemic antibiotics for the case and prophylactic rifampicin for close contacts The patient's 5 year-old sister, 5-year-old female developed sepsis with a characteristic petechial and purpuric rash which began on third days after her brother's illness). her blood and throat cultures were taken after she had received rifampicin chemoprophylaxis and no pathogen was identified.
Bigham et al., 2001 (Canada)	30	Case study	A case of PMC in a child with evidence of transmission to the mother, who subsequently died of IMD. Cultures from the child and mother were both positive for *N.meningitidis* serogroup C:2a:P10.2
Reports of identical strains from PMC cases and screening of their household or close contacts in the absence of invasive disease			
Citation	Ref No.	Study type	Key results
Stuart and McWalter, 1948 (Scotland)	27	Case series	Six cases of PMC in children aged 9 weeks to 10 years; 2/6 cases had close contacts with positive postnasal cultures – both were family members of the cases
Mangiaracine and Pollen, 1944 (USA)	26	Case series	Nasopharyngeal swab from the mother of one child with PMC grew an identical strain as the one causing conjunctivitis
Brook et al., 1979 (USA)	4	Case report	Throat swab were taken from a 19-year-old woman with PMC and 7 close contacts; an identical strain was identified from 1/7 contacts; neither the case nor the close contacts were given systemic antibiotics
Lewis and Ferris, 1948 (Australia)	28	Case report	An infant with bilateral PMC was treated with oral penicillin and sulphacetamide drops; both parents of the infant and a visiting uncle carried the same meningococcal strain as the infant
Kahaner and Lanou, 1945 (USA)	29	Case report	An infant with unilateral PMC had the same meningococcal type isolated from nose and throat cultures of the father

such as cefotaxime if Gram-negative diplococci are seen on the eye swab, until the pathogen is identified; subsequent antibiotic treatment can then be optimised accordingly.[32,33]

(iii) *What is the duration of oral antibiotic treatment in an otherwise well child with PMC and no systemic symptoms?*

The current UK guidelines recommend seven days of intravenous ceftriaxone for the treatment of IMD.[11] For PMC, the duration of systemic antibiotic treatment in the literature varied from 5 days of oral penicillin[15] to 10 days of oral cefprozil.[30] Like IMD cases, patients with PMC who are treated with antibiotics other than intravenous cephalosporins should also receive ciprofloxacin

chemoprophylaxis to eradicate carriage and, therefore, interrupt potential transmission to close contacts in the future. The recent EU-wide restrictions precautions on the use of systemic fluoroquinolone antibiotics (including ciprofloxacin) due to very rare reports of serious side-effects does not apply to the single dose of ciprofloxacin recommended for chemoprophylaxis of meningococcal disease.[34]

Chemoprophylaxis and meningococcal vaccination for close contacts

Close contacts of patients with IMD have a 1 in 300 (0.3%) risk of invasive disease when antibiotic chemoprophylaxis is not administered; this is more than 300 times the incidence of sporadic invasive disease in the general population.[35] The rationale behind giving antibiotic prophylaxis to close contacts of IMD is to eliminate carriage of meningococci from the close contact group and thus reduce onward transmission. In doing so, the risk of secondary cases in close contacts is reduced by up to 89%[36]

Although rare, the small but significant risk of severe invasive disease among close contacts of PMC cases with several reported fatalities would justify a recommendation for antibiotic chemoprophylaxis for this group. The serogroups responsible for PMC will depend on the circulating strains in that region, and all the major serogroups have been reported to cause PMC (Table). There have also been reports of PMC caused by non-groupable meningococci, which are generally considered to be less virulent, in immunocompetent individuals and, therefore, unlikely to become invasive in the case or their close contacts. Systemic antibiotic treatment of the PMC case and antibiotic chemoprophylaxis for the close contacts should, however, be initiated as soon as *Neisseria meningitidis* is identified to be responsible for the conjunctivitis.

There is currently no evidence for or against offering meningococcal vaccination to PMC cases or their close contacts. Vaccinating the PMC case and close contacts, however, is unlikely to offer any additional protection because meningococcal transmission should have been interrupted by treating the case with appropriate antibiotics and offering chemoprophylaxis to the close contacts.

Conclusions

Primary meningococcal conjunctivitis is rare, with incidence ranging from <0.08% to 2% of all acute conjunctivitis cases, although the true incidence is likely to be underestimated because microbiological investigations are not routinely performed for uncomplicated conjunctivitis cases. Unlike other causes of conjunctivitis, around 10–29% of PMC patients go on to develop IMD. Those who are treated with systemic antibiotics in addition to topical antibiotics alone, however, are significantly less likely to develop IMD compared to those treated with topical antibiotics alone. Clinicians need to be aware of the need to treat PMC cases with systemic antibiotics. Additionally, close contacts of PMC cases may rarely go on to develop severe and potentially fatal invasive disease which can be prevented through appropriate antibiotic chemoprophylaxis, as currently offered to close contacts of IMD cases. Meningococcal vaccination of the PMC case or close contacts is unlikely to offer any additional protection after appropriate antibiotic treatment and prophylaxis, respectively. These findings specific to PMC cases and their close contacts need to be highlighted in the relevant clinical and public health guidelines for the management of sporadic cases of meningococcal disease.

Funding source

No funding.

Declaration of Competing Interest

SNL performs contract research for vaccine manufacturers (including GSK, Pfizer, and Sanofi Pasteur) on behalf of St George's University of London and Public Health England but receive no personal remuneration. The Immunisation and Countermeasures Department has provided GSK with post-marketing surveillance reports on meningococcal, *Haemophilus influenzae*, and pneumococcal infections, which the companies are required to submit to the UK Licensing Authority in compliance with their Risk Management Strategy. A cost recovery charge is made for these reports. All other authors: no conflict.

Acknowledgments

We would like to thank colleagues in the Knowledge and Library Services at Public Health England for their assistance in acquiring articles pertinent to this work. We would also like to thank both the immunisation department and the meningococcal reference unit for their ongoing help and support in the national surveillance of invasive meningococcal disease.

References

1. Poulos RG, Smedley EJ, Ferson MJ, Bolisetty S, Tapsall JW. Refining the public health response to primary meningococcal conjunctivitis. *Commun Dis Intell Q Rep* 2002;**26**(4):592–5.
2. Chacon-Cruz E, Alvelais-Palacios JA, Rodriguez-Valencia JA, Lopatynsky-Reyes EZ, Volker-Soberanes ML, Rivas-Landeros RM. Meningococcal neonatal purulent conjunctivitis/sepsis and asymptomatic carriage of *N. meningitidis* in mother's vagina and both parents' nasopharynx. *Case Rep Infect Dis* 2017;**2017**:6132857.
3. Barquet N, Gasser I, Domingo P.A. Moraga F., Macaya A., Elcuaz R. Primary meningococcal conjunctivitis: report of 21 patients and review 1990. 838–47.
4. Brook I. Anaerobic and aerobic bacterial flora of acute conjunctivitis in children. *Arch Ophthalmol (Chicago, Ill: 1960)* 1980;**98**(5):833–5.
5. Stirland RM, Tooth JA, Meigh JA. Acute bacterial conjunctivitis and maltose negative meningococci. *J Clin Pathol* 1984;**37**(12):1416.
6. Kenny JF. Meningococcal conjunctivitis in neonates. *Clin Pediatr (Phila)* 1987;**26**(9):473–6.
7. England P.H. Guidance for the public health management of meningococcal disease in the UK. In: Immunisations, edition. London, UK: Public Health England; 2018.
8. Australia CDN *Invasive meningococcal disease CDNA national guidlines for public health units*. 12 edition. Australia: Department of Health; 2017. p. 20.
9. Prevention CfDCa. *Chapter 14: meningococcal disease. Pink book: epidemiology and prevention of vaccine-preventable diseases*. 13th edition. USA: Centers for Disease Control and Prevention; 2019.
10. Optometrists TCo. Conjunctivitis (Bacterial): the college of optometrists; 2018 [updated 20/12/2018. Available from: https://www.college-optometrists.org/guidance/clinical-management-guidelines/conjunctivitis-bacterial-.html.
11. NICE. *Bacterial meningitis and meningococcal septicaemia: management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care*. RCOG Press; 2010.
12. Committee JF. *Eye, Infections London*. BMJ Group and Pharmaceutical Press; 2019. [updated 30/08/2019. Available from: *https://bnf.nice.org.uk/treatment-summary/eye-infections.html*.
13. England PH. *Guidance for public health management of meningococcal disease in the UK: updated August 2019*. London, UK: Public Health England; 2019.
14. Control ECfDPa. *Public health management of sporadic cases of invasive meningococcal disease and their contacts*. Stockholm: ECDC; 2010.
15. Newton DA, Wilson WG. Primary meningococcal conjunctivitis. *Pediatrics* 1977;**60**(1):104–6.
16. Odegaard A. Primary meningococcal conjunctivitis followed by meningitis and septicemia. *NIPH Ann* 1983;**6**(1):55–7.
17. Stansfield RE, Masterton RG, Dale BA, Fallon RJ. Primary meningococcal conjunctivitis and the need for prophylaxis in close contacts. *J Infect* 1994;**29**(2):211–14.
18. Ellis M, Weindling AM, Davidson DC, Ho N, Damjanovic V. Neonatal meningococcal conjunctivitis associated with meningococcal meningitis. *Arch Dis Child* 1992;**67**(10 Spec No):1219–20.
19. Reese FM. Meningococcus conjunctivitis followed by septicemia and beginning meningitis: a case report. *Am J Ophthalmol* 1936;**19**(9):780–2.
20. Irani F, Ruddell T. Meningococcal conjunctivitis. *Aust N Z J Ophthalmol* 1997;**25**(2):167–8.
21. Moraga Llop FA, Barquet Esteve N, Domingo Pedrol P, Gallart Catala A. Primary meningococcal conjunctivitis: implications beyond the conjunctiva. *Med Clin (Barc)* 1996;**107**(4):130–2.
22. Dillman CE Jr. Meningococcemia following meningococcal conjunctivitis. *South Med J* 1967;**60**(5):456 passim.

23. Nussbaum E, Jeyaranjan T, Feldman F. Primary meningococcal conjunctivitis followed by meningitis. *J Pediatr* 1978;**92**(5):784–5.
24. Curran JP, Nunez JR, Visconti E. Primary meningococcal conjunctivitis. *NY State J Med* 1989;**11**:684–5.
25. Neoh C, Agius-Fernandez A, Kaye SB, Molyneux EM, Hart CA. Primary meningococcal conjunctivitis in children. *Br J Clin Pract* 1994;**48**(1):27–8.
26. Mangiaracine AB, Pollen A. Meningococcic conjunctivitis. *JAMA Ophthalmol* 1944;**31**(4):284–8.
27. Stuart RD, McWalter D. Primary meningococcal conjunctivitis in children. *Lancet* 1948;**251**(6494):246–9.
28. Lewis N, Ferris AA. A case of primary meningococcal conjunctivitis. *Med J Aust* 1948;**1**(20):621–2.
29. Kahaner JR, Lanou WW. Exogenous meningococcic conjunctivitis. *NY State J Med* 1945;**45**:1687–8.
30. Bigham JM, Hutcheon ME, Patrick DM, Pollard AJ. Death from invasive meningococcal disease following close contact with a case of primary meningococcal conjunctivitis–Langley, British Columbia, 1999. *Can Commun Dis Rep* 2001;**27**(2):13–18.
31. McAnena L, Knowles SJ, Curry A, Cassidy L. Prevalence of gonococcal conjunctivitis in adults and neonates. *Eye (Lond)* 2015;**29**(7):875–80.
32. Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. *MMWR recommendations and reports: Morbidity and mortality weekly report recommendations and reports* 2015;**64**(Rr-03):1–137.
33. Diseases ACOIKimberlin DW, Brady MT, Jackson MA, editors*Red Book*; 2018. 2018 p. 1153.
34. Agency EM. *Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics*. The Netherlands: European Medicines Agency; 2019.
35. Zangwill KM, Schuchat A, Riedo FX, Pinner RW, Koo DT, Reeves MW, et al. School-based clusters of meningococcal disease in the United States. Descriptive epidemiology and a case-control analysis. *JAMA* 1997;**277**(5):389–95.
36. Purcell B, Samuelsson S, Hahné SJM, Ehrhard I, Heuberger S, Camaroni I, et al. Effectiveness of antibiotics in preventing meningococcal disease after a case: systematic review. *BMJ* 2004;**328**(7452):1339.

Study 8: Lower risk of invasive meningococcal disease during pregnancy; national prospective surveillance in England, 2011-2014 *British Journal of Obstetrics and Gynaecology* (2019)

BJOG An International Journal of Obstetrics and Gynaecology

DOI: 10.1111/1471-0528.15701
www.bjog.org

Maternal medicine

Lower risk of invasive meningococcal disease during pregnancy: national prospective surveillance in England, 2011–2014

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Accepted 22 March 2019. Published Online 8 May 2019.

Objective To describe cases of invasive meningococcal disease (IMD) in women of childbearing age and to estimate the disease incidence and relative risk of IMD in pregnant compared with non-pregnant women.

Design Prospective enhanced national surveillance for IMD.

Setting England.

Population Women of reproductive age (15–44 years) with laboratory-confirmed IMD.

Methods Public Health England conducts enhanced national surveillance for IMD in England. Laboratory-confirmed cases are followed up with postal questionnaires to general practitioners. All cases confirmed in women of reproductive age from 1 January 2011 to 31 December 2014 were included.

Main outcome measures Annual IMD incidence and relative risk of IMD in pregnant compared with non-pregnant women of reproductive age.

Results During the 4-year surveillance period, there were 1502 cases of IMD in females across England; of these, 310 (20.6%) cases were in women of reproductive age, including four women who were pregnant at the time of IMD confirmation (1.3%). Serogroup distribution of IMD cases in women of childbearing age was similar to the overall distribution. The four cases in otherwise healthy pregnant women were confirmed across all trimesters and all survived; one case in the first trimester had a septic miscarriage. The incidence of IMD was lower in pregnant than in non-pregnant women (0.16 compared with 0.76 per 100 000 pregnant and non-pregnant years, respectively), giving a lower risk of IMD in pregnant women (incidence rate ratio, IRR, 0.21; 95% confidence interval, 0.06–0.54).

Conclusions Pregnant women are nearly five times less likely to develop IMD compared with non-pregnant women, but the infection can be severe.

Keywords Invasive meningococcal disease, meningococcal disease, pregnancy.

Tweetable abstract The risk of meningococcal disease is lower in pregnant women compared with non-pregnant women; the infection can occur across all trimesters and can be severe.

Please cite this paper as: Parikh SR, Borrow R, Ramsay ME, Ladhani SN. Lower risk of invasive meningococcal disease during pregnancy: national prospective surveillance in England, 2011–2014. BJOG 2019;126:1052–1057.

Introduction

Neisseria meningitidis is a Gram-negative coccobacterium that has the propensity to cause invasive meningococcal disease (IMD). The disease is one of the leading causes of bacterial meningitis and septicaemia worldwide, and is associated with high morbidity and mortality. The pathogen's polysaccharide capsule is its most important virulence factor. It is also used to characterise the bacteria into 12 serogroups, including five that are responsible for nearly all invasive infections globally: A, B, C, W, and Y.[1,2] *Neisseria meningitidis* is an accidental pathogen: it is usually carried in the nasopharynx of healthy individuals, particularly adolescents and young adults, and only causes invasive disease when transmitted to susceptible individuals. An increased risk of IMD in individuals with complement deficiencies, asplenia, and HIV is well documented.[3–6]

Pregnancy is associated with an immunocompromised state and pregnant women have a significantly higher risk of some severe bacterial and viral infections compared with non-pregnant women.[7] IMD in pregnancy is extremely rare, and publications are mainly restricted to individual

case reports, ranging from mild infection in the mother to fatal meningococcaemia for both the mother and unborn child. [8,9]

Whether pregnant women themselves are at increased risk of IMD compared with non-pregnant women is not known. A previous Dutch study reported an increased risk of meningococcal disease in children whose mothers were pregnant,[10] but a US study reported no significant difference in meningococcal carriage in relation to pregnancy status.[11] In England, Public Health England (PHE) conducts enhanced national surveillance of IMD. The objective of this study was to estimate the risk of IMD in pregnant women compared with non-pregnant women, and to describe the epidemiology, clinical characteristics, and outcomes of IMD in pregnant women in England over a 4-year period.

Methods

Surveillance of IMD

Public Health England (PHE) conducts enhanced national IMD surveillance and provides a national reference service for IMD confirmation and characterisation of invasive meningococci (both culture and non-culture).[12] The PHE Meningococcal Reference Unit (MRU) also provides a free national polymerase chain reaction (PCR) testing service for clinical samples from patients with suspected IMD across England. More than 10 000 samples are PCR-tested every year, with a 6% positivity rate. This redundancy ensures high case ascertainment for national surveillance of such a rare disease. In 2012, PHE enhanced the laboratory surveillance by requesting general practitioners (GPs) to complete a short clinical questionnaire for all laboratory-confirmed IMD cases diagnosed in England since 1 January 2011. National surveillance data were used for this study and, therefore, patients were not involved in the development of the analysis plan. All laboratory-confirmed IMD cases in women of reproductive age (15–44 years) in England from 1 January 2011 to 31 December 2014 (4 years) were included. Women in this cohort would have been eligible for the national MenC immunisation programme that has been in place since 1999; there was no MenB or MenACWY immunisation programme during this period.[13]

Information collected included comorbidities, clinical presentation, intensive care admission, and outcomes. Incomplete or missing information in the questionnaires was followed up by telephoning the GP, contacting the patient's hospital clinician, or requesting additional information from the local PHE health protection team (HPT), which maintains records of all suspected and confirmed IMD cases for the public health management of cases and close contacts, and for monitoring outbreaks. If needed, additional information was sought from HPZone, a national web-based case management system used by PHE HPTs to record public health events and actions, and from electronic death registration records provided to PHE by the Office for National Statistics (ONS) for public health surveillance purposes. For fatal cases, the date of death was confirmed using the Personal Demographics Service (PDS). Online annual reports of the Confidential Enquiry into Maternal Deaths (CEMD, www.npeu.ox.ac.uk/mbrrace-uk/reports/confidential-enquiry-into-maternal-deaths) were also accessed to identify any pregnancy-related deaths resulting from IMD during the surveillance period. The HPZone records for neonatal IMD cases confirmed during the surveillance period were checked for any mention of maternal illness during the perinatal period. Data from ONS on population and maternity (including total conceptions) were used for denominator populations.[14,15] Pregnant years were estimated as the product of the total number of conceptions between 2011 and 2014 and the maximum possible gestation period (9 months). This was then used to estimate non-pregnant years as the difference between the total female population aged 15–44 years and pregnant years.

Data

Demographic, clinical questionnaire, and microbiological data were entered into a single Microsoft Access Database (Microsoft Corporation, Redmond, WA, USA), cleaned, and de-duplicated before importing into STATA 13.0 (StataCorp LP, College Station, TX, USA) for analysis. In addition to describing the demographics and clinical characteristics of pregnant women with laboratory-confirmed IMD, the core outcomes included estimating IMD incidence rates with Poisson 95% confidence intervals for pregnant and non-pregnant women along with incidence rate ratios for pregnant versus non-pregnant women.

Results

Between 2011 and 2014 (317 417 121 woman-years), there were 2980 laboratory-confirmed IMD cases in England. Clinical information was available for all 2980 cases. There were 2245 (75.3%) MenB, 309 MenY (10.4%), 265 MenW (8.9%), and 117 MenC (3.9%) cases, with an additional 44 (1.5%) cases resulting from rarer serogroups. There were 1502 IMD cases in females across England during the 4-year surveillance period; of these, 310 (20.6%) cases were in women of reproductive age (median age, 20 years; Q1, 18 years; Q3, 28.5 years).

The serogroup distribution of IMD cases in women of reproductive age was similar to the overall distribution, with most cases caused by MenB (n = 218, 70.3%), followed by MenW (n = 33, 10.6%), MenY (n = 33, 10.6%), MenC (n = 21, 6.8%), and rare serogroups (n = 5, 1.6%).

None of the cases in this cohort had received the MenB vaccine 4CMenB (Bexsero®; GSK, Rixensart, Belgium), and there were no cases of vaccine failure among those with MenW, MenY, or MenC disease. Clinical presentation varied: meningitis (126/310 cases; 40.6%) was the most prevalent clinical presentation, followed by septicaemia (103/310; 33.2%), both meningitis and septicaemia (70/310; 22.6%), pneumonia (8/301; 2.6%), septic arthritis (2/310; 0.7%), and soft tissue infection (1/301; 0.3%). Nearly half of the women (128/310; 41.3%) required intensive care admission and 19 (6.1%) women died. Five women (1.6%) had reported complement deficiency and seven (2.3%) had reported immunosuppression or malignancy. None of the women who died of IMD had an underlying comorbidity.

Pregnant women

Among the cohort of 310 women of reproductive age, four (1.3%) were reported to be pregnant at the time of infection, including two cases of MenY and one case each of MenB and MenC disease. We did not identify any additional pregnancy-related cases or deaths as a result of IMD during the surveillance period from any of the additional data sources. Five cases of early-onset neonatal IMD (within 7 days of birth) were reported over the surveillance period; the HPZone records for these cases did not report any maternal illness during the perinatal period. All four IMD cases diagnosed during pregnancy were confirmed by culture only. The four women had different clinical presentations, and none had underlying risk factors for meningococcal disease (Table 1). Cases occurred across all trimesters: there was a single case in the first trimester in which the mother survived but had a septic miscarriage at the time of infection; the other three women recovered uneventfully from their infection and carried their pregnancies to term.

The estimated incidence of IMD in pregnant women was 0.16/100 000 pregnant woman-years compared with 0.76/100 000 non-pregnant woman years in non-pregnant women in the same age group (incidence rate ratio, IRR, 0.21; 95% confidence interval, 95% CI, 0.06–0.54; $P < 0.0001$). Therefore, pregnant women were nearly five times less likely to develop IMD than non-pregnant women.

Table 1. Incidence of laboratory-confirmed invasive meningococcal disease (IMD) and disease characteristics among all females ($n = 1502$), and among pregnant ($n = 4$) and non-pregnant ($n = 306$) women, across England during 2011–2014

	All females	IMD in women aged 15–44 years	
	$n = 1502$	Non-pregnant $n = 306$	Pregnant $n = 4$
Incidence	1.38 per 100 000 female years	0.76 per 100 000 non-pregnant woman years	0.16 per 100 000 pregnant woman years
Capsular group			
B	1090 (72.6)	217 (70.9)	1 (25)
C	62 (4.1)	20 (6.5)	1 (25)
W	147 (9.8)	33 (10.8)	0 (0)
Y	183 (12.2)	31 (10.1)	2 (50)
Other	20 (1.3)	5 (1.6)	0 (0)
Clinical presentation			
Meningitis	380 (25.3)	125 (40.8)	1 (25)
Septicaemia	695 (46.3)	102 (33.3)	1 (25)
Meningitis and septicaemia	306 (20.4)	69 (22.5)	1 (25)
Pneumonia	79 (5.3)	7 (2.3)	1 (25)
Septic arthritis	24 (1.6)	2 (0.7)	0 (0)
Other	18 (1.2)	1 (0.3)	0 (0)
Underlying comorbidity			
Malignancy/ immunosuppression	54 (3.6)	7 (2.3)	0 (0)
Complement deficiency	8 (0.5)	5 (1.6)	0 (0)
Asplenia	2 (0.1)	0 (0)	0 (0)
Diseases severity			
Intensive care admission	464 (30.9)	125 (40.8)	3 (75)
Outcome			
Died within 28 days	107 (7.1)	19 (6.2)	0 (0)

Discussion

Main findings

Invasive meningococcal disease (IMD) is rare in pregnancy, and pregnant women are five times less likely to develop IMD compared to non-pregnant women. Only four pregnant women developed IMD across England over the 4 years of surveillance. IMD occurred across all three trimesters; one case in the first trimester was associated with septic miscarriage at the time of infection. All four pregnant women survived their infection.

Strengths and limitations

The strength of this study lies in the high case ascertainment of IMD through the national enhanced surveillance in England, with clinical follow-up of all confirmed cases since 2011. National surveillance does not include probable IMD cases that are not culture- or PCR-confirmed. Such cases, however, are likely to be rare given the large volume of PCR-testing conducted by PHE MRU, the high sensitivity of PCR testing, and the redundancy of the testing service (only 6% positivity). Major life events such as pregnancy and IMD are likely to be documented in the GP records and, therefore, under-reporting of pregnancy status among IMD cases (which could potentially explain the lower IMD risk in pregnancy estimated in this study) is

unlikely. Additionally, the denominator for the IRR analysis (pregnancy-years) included the total number of conceptions but not miscarriages; including miscarriages in the denominator would have lowered the estimated IMD incidence among pregnant women and, therefore, lowered the IRR between pregnant and non-pregnant women. One limitation of our study, however, was the limited collection of detailed clinical information, which may have been useful for clinicians managing such rare cases during pregnancy.

Interpretation of findings

Pregnancy is often considered a general condition of immunosuppression, where the placental immune response and its tropism for specific pathogens affect the pregnant woman's susceptibility to and severity of certain infectious diseases.[16] For example, we have recently shown that pregnancy is associated with a higher risk of non-typeable *Haemophilus influenzae* (ntHi) disease, and that this infection is associated with poor pregnancy outcomes,[17] whereas others have found a 13- to 100-fold higher risk of listeriosis,[18–20] and a two-fold increased incidence of invasive group B streptococcus (GBS) disease, compared with non-pregnant women of similar age.[21] The latter study also found that postpartum women had a 20-fold higher incidence of GBS and group A streptococcus (GAS) disease compared with non-pregnant women. IMD is an extremely rare cause of postpartum sepsis,[22–24] and we did not identify any IMD case during the postpartum period in our surveillance. Given the severe nature of IMD, this information would be expected to have been documented in the GP records and therefore reported through the surveillance questionnaires.

Invasive bacterial infection is associated with high morbidity and mortality for the pregnant woman and the fetus. In our recent study of invasive ntHi disease, infection during the first 24 weeks of pregnancy was invariably associated with fetal loss or extremely premature birth, whereas infection during the second half of pregnancy was associated with premature birth or stillbirth in up to a third of cases.[17]

We identified only a few published case reports of IMD in pregnant women, with varying clinical manifestations and outcomes. Reports of acute infection include, but are not limited to, primary meningococcal pericarditis,[25] endocervicitis,[8] sepsis during labour,[26] and fulminating meningococcal septicaemia.[27] Chronic meningococcaemia has also been reported in pregnancy;[28] this is an uncommon manifestation of IMD that is associated with meningococcal *lpxL1* gene mutations,[29] resulting in inactivated endotoxin.[30] In all reported cases, both the mother and infant recovered uneventfully, which is consistent with older reports of cases from the 1930s and 1940s.[27]

We have, for the first time, shown that pregnant women have a lower risk of IMD compared with non-pregnant women in the same age group. Interestingly, a previous retrospective matched case–control study during 1990–2002 found that the mothers of children with IMD were 11.7 (95% CI, 2.6–53.9) times more likely to be pregnant compared with control children who did not have IMD.[10] The authors postulated that pregnant women might undergo immunological changes leading to higher meningococcal carriage, as reported in one carriage study of household contacts of children with IMD.[31] A more recent study, however, found that only one of 100 pregnant women, and none of 99 non-pregnant women were meningococcal carriers.[11]

We hypothesise that pregnant women may be at lower risk of IMD because of changes in their social interaction with others, resulting in a lower exposure to meningococcal carriers. Transmission between sexual partners during pregnancy has been reported, however: in a published case report, the partner of a woman with meningococcal endocervicitis during pregnancy had an identical strain isolated from a throat swab.[8] Having other children in the household – especially older teenagers, who have the highest meningococcal carriage rates – could potentially be another transmission source.[32] Unfortunately, we do not have any information on the carriage status of any of the close contacts for the four cases in our cohort, who were all relatively young (age range, 21–32 years). The current UK national guidelines recommend that all close contacts of probable or confirmed IMD cases should receive antibiotic chemoprophylaxis as soon as possible to prevent additional secondary cases.[33] Meningococcal carriage studies among household contacts of confirmed cases in pregnant women and newborn infants could provide useful insights into modes of transmission and potential strategies for prevention.

Neisseria meningitidis is usually carried in the nasopharynx, especially among adolescents; what is less well-reported, however, is the meningococcal colonisation of the genitourinary tract, which has been associated with intrauterine and perinatal infection, and can cause severe illness in newborn infants. Meningococcal infections of the genitourinary tract and anal canal have been reported, with recovery of the meningococcus from the urethra, the anal canal of men, and the cervix of women.[34] There have been 46 reports of neonatal IMD, some with presumed maternal infection,[35] and others with vaginal colonisation without systemic disease in the mother.[36] In a recent case of neonatal MenY sepsis, the same serogroup was isolated from the mother's vagina and the nasopharynx of both parents.[37] Others have provided molecular evidence confirming identical strains carried by the mother and causing invasive disease in her infant, with multiple reports of fatal intrauterine and perinatal infection with the same strain.[9,36,38–40] Less severe manifestations of meningococcal

disease, such as conjunctivitis and osteomyelitis, have also been reported in neonates.[41–43]

There is a growing interest in meningococcal strains acquiring adaptive genes to permit survival in anaerobic conditions, making sexual transmission possible.[44] In a recent outbreak of invasive MenC disease among men who have sex with men (MSM), the responsible MenC strains were found to harbour an intact *aniA* gene coding for a nitrite reductase that permits survival in micro-anaerobic environments, potentially allowing sexual transmission among MSM through urogenital colonisation.[22]

Conclusion

The risk of IMD is significantly lower in pregnant women compared with non-pregnant women in the same age group, with around one case diagnosed per year in England. The lower risk may be the result of changes in social interaction leading to a lower risk of exposure to meningococcal carriers. Clinicians need to be aware of the ability of meningococci to colonise and infect the urogenital and anal tracts, which could be a potential source of transmission through sexual contact and/or childbirth.

Disclosure of interests

SNL and RB perform contract research for vaccine manufacturers on behalf of St. George's University of London and Public Health England, respectively, but receive no personal remuneration. The Immunisation and Countermeasures Division of PHE, where all of the authors are employees, regularly provides vaccine manufacturers with post-marketing surveillance reports on meningococcal, *Haemophilus influenzae*, and pneumococcal infections, which the companies are required to submit to the UK Licensing authority in compliance with their Risk Management Strategy. A cost recovery charge is made for these reports. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

SNL and MER conceived the idea for the study; SRP collected all of the data, performed the analysis, and wrote the first draft of the manuscript; SRP, MER, RB, and SNL contributed to the interpretation and discussion of the results.

Details of ethics approval

PHE has legal permission, provided by Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002, to process patient confidential information for the national surveillance of communicable diseases (www.legislation.gov.uk/uksi/2002/1438/regulation/3/made). This includes PHE's responsibility to monitor the safety and effectiveness of vaccines, and as such individual patient consent is not required.

Funding

None.

Acknowledgements

The authors would like to thank all staff in the Immunisations department and at the MRU for their assistance with all work related to the enhanced surveillance of IMD in the UK. Acknowledgements are also extended to Kim Taylor, Tracey Smeulders, and Rehana Shivji for facilitating patient follow-up and data entry.■

References

1 Halperin SA, Bettinger JA, Greenwood B, Harrison LH, Jelfs J, Ladhani SN, et al. The changing and dynamic epidemiology of meningococcal disease. *Vaccine* 2012;30(Suppl 2):B26–36.
2 Bettinger JA, Scheifele DW, Halperin SA, Vaudry W, Findlow J, Borrow R, et al. Diversity of Canadian meningococcal serogroup B isolates and estimated coverage by an investigational meningococcal serogroup B vaccine (4CMenB). *Vaccine* 2013;32:124–30.
3 Figueroa J, Andreoni J, Densen P. Complement deficiency states and meningococcal disease. *Immunol Res* 1993;12:295–311.
4 Krivit W. Overwhelming postsplenectomy infection. *Am J Hematol* 1977;2:193–201.
5 Eraklis AJ, Kevy SV, Diamond LK, Gross RE. Hazard of overwhelming infection after splenectomy in childhood. *N Engl J Med* 1967;276:1225–9.
6 Simmons RD, Kirwan P, Beebeejaun K, Riordan A, Borrow R, Ramsay ME, et al. Risk of invasive meningococcal disease in children and adults with HIV in England: a population-based cohort study. *BMC Med* 2015;13:297.
7 Kourtis AP, Read JS, Jamieson DJ. Pregnancy and infection. *N Engl J Med* 2014;370:2211–8.
8 Harriau P, Ramanantsoa C, Pierre F, Riou JY, Quentin R. Endocervical infection in a pregnant woman caused by *Neisseria meningitidis*: evidence of associated oropharyngeal colonization of the male partner. *Eur J Obstet Gynecol Reprod Biol* 1997;74:145–7.
9 Polayes SH, Ohlbaum C, Winston HB. Meningococcus meningitis with massive hemorrhage of the adrenals (Waterhouse-Friderichsen syndrome) complicating pregnancy with pre-eclamptic toxemia. *Am J Obstet Gynecol* 1953;65:192–6.
10 van Gils EJ, van Woensel JB, van der Ende A, Kuijpers TW. Increased attack rate of meningococcal disease in children with a pregnant mother. *Pediatrics* 2005;115:e590–3.
11 Knudtson EJ, Lytle ML, Vavricka BA, Skaggs VS, Peck JD, Elimian AE. A comparison of meningococcal carriage by pregnancy status. *J Negat Results Biomed* 2010;9:6.
12 Gray SJ, Trotter CL, Ramsay ME, Guiver M, Fox AJ, Borrow R, et al. Epidemiology of meningococcal disease in England and Wales 1993/94 to 2003/04: contribution and experiences of the Meningococcal Reference Unit. *J Med Microbiol* 2006;55:887–96.
13 Findlow H, Campbell H, Lucidarme J, Andrews N, Linley E, Ladhani S, et al. Serogroup C *Neisseria meningitidis* disease epidemiology, seroprevalence, vaccine effectiveness and waning immunity, England, 1998/99 to 2015/16. *Euro Surveill* 2019;24:1–11. https://doi.org/10.2807/1560-7917.ES.2019.24.1.1700818

14 Office for National Statistics. Population estimates analysis tool. Office for National Statistics; 2017[www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesanalysistool]. Accessed 02 May 2019.

15 Office for National Statistics. Conception statistics, England and Wales. Office for National Statistics; 2018[www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/conceptionandfertilityrates/datasets/conceptionstatisticsenglandandwalesreferencetables]. Accessed 02 May 2019.

16 Mor G, Cardenas I. The immune system in pregnancy: a unique complexity. *Am J Reprod Immunol* 2010;63:425–33.

17 Collins S, Ramsay M, Slack MP, Campbell H, Flynn S, Litt D, et al. Risk of invasive *Haemophilus influenzae* infection during pregnancy and association with adverse fetal outcomes. *JAMA* 2014;311:1125–32.

18 Mylonakis E, Paliou M, Hohmann EL, Calderwood SB, Wing EJ. Listeriosis during pregnancy: a case series and review of 222 cases. *Medicine (Baltimore)* 2002;81:260–9.

19 Pouillot R, Hoelzer K, Jackson KA, Henao OL, Silk BJ. Relative risk of listeriosis in Foodborne Diseases Active Surveillance Network (FoodNet) sites according to age, pregnancy, and ethnicity. *Clin Infect Dis* 2012;54(Suppl 5):S405–10.

20 Goulet V, Hebert M, Hedberg C, Laurent E, Vaillant V, De Valk H, et al. Incidence of listeriosis and related mortality among groups at risk of acquiring listeriosis. *Clin Infect Dis* 2012;54:652–60.

21 Deutscher M, Lewis M, Zell ER, Taylor TH Jr, Van Beneden C, Schrag S. Incidence and severity of invasive *Streptococcus pneumoniae*, group A *Streptococcus*, and group B *Streptococcus* infections among pregnant and postpartum women. *Clin Infect Dis* 2011;53:114–23.

22 Hellenbrand W, Claus H, Schink S, Marcus U, Wichmann O, Vogel U. Risk of invasive meningococcal disease in men who have sex with men: lessons learned from an outbreak in Germany, 2012–2013. *PLoS One* 2016;11:e0160126.

23 Finan MA, Smith SG, Sinnott JT, O'Brien W, Ibach M, Morales R. An interesting case presentation: peripartum meningococcal meningitis. *J Perinatol* 1992;12:78–80.

24 Morgan JR, Fedder J, Smith JA. Letter: postpartum infection with meningococcemia. *Can Med Assoc J* 1976;114:294.

25 Braester A, Nusem D, Horn Y. Primary meningococcal pericarditis in a pregnant woman. *Int J Cardiol* 1986;11:355–8.

26 Neubert AG, Schwartz PA. *Neisseria meningitidis* sepsis as a complication of labor. A case report. *J Reprod Med* 1994;39:749–51.

27 Brandeberry KR, Vergon JM. Meningococcic meningitis in term pregnancy. *Am J Obstet Gynecol* 1951;61:699–700.

28 Persa O-D, Jazmati N, Robinson N, Wolke M, Kremer K, Schweer K, et al. A pregnant woman with chronic meningococcaemia from *Neisseria meningitidis* with lpxL1-mutations. *Lancet* 2014;384:1900.

29 Harwood CA, Stevens JC, Orton D, Bull RC, Paige D, Lessing MP, et al. Chronic meningococcaemia: a forgotten meningococcal disease. *Br J Dermatol* 2005;153:669–71.

30 Fransen F, Heckenberg SG, Hamstra HJ, Feller M, Boog CJ, van Putten JP, et al. Naturally occurring lipid A mutants in *Neisseria meningitidis* from patients with invasive meningococcal disease are associated with reduced coagulopathy. *PLoS Pathog* 2009;5:e1000396.

31 Frasch CE, Mocca LF. Strains of *Neisseria meningitidis* isolated from patients and their close contacts. *Infect Immun* 1982;37:155–9.

32 Christensen H, May M, Bowen L, Hickman M, Trotter CL. Meningococcal carriage by age: a systematic review and meta-analysis. *Lancet Infect Dis* 2010;10:853–61.

33 England PH. Guidance on the prevention and management of meningococcal meningitis and septicaemia in higher education institutions: raising awareness, promoting immunisation and planning ahead. London: Public Health England; 2017[www.universitiesuk.ac.uk/policy-and-analysis/reports/Pages/prevention-management-meningococcal-meningitis-septicaemia-higher-education.aspx]. Accessed 02 May 2019.

34 Givan KF, Thomas BW, Johnston AG. Isolation of *Neisseria meningitidis* from the urethra, cervix, and anal canal: further observations. *Br J Vener Dis* 1977;53:109–12.

35 Sunderland WA, Harris HH, Spence DA, Lawson HW. Meningococcemia in a newborn infant whose mother had meningococcal vaginitis. *J Pediatr* 1972;81:856.

36 Jones RN, Slepack J, Eades A. Fatal neonatal meningococcal meningitis: association with maternal cervical-vaginal colonization. *JAMA* 1976;236:2652–3.

37 Chacon-Cruz E, Alvelais-Palacios JA, Rodriguez-Valencia JA, Lopatynsky-Reyes EZ, Volker-Soberanes ML, Rivas-Landeros RM. Meningococcal neonatal purulent conjunctivitis/sepsis and asymptomatic carriage of *N. meningitidis* in mother's vagina and both parents' nasopharynx. *Case Rep Infect Dis* 2017;2017:6132857.

38 Bhutta ZA, Khan IA, Agha Z. Fatal intrauterine meningococcal infection. *Pediatr Infect Dis J* 1991;10:868–9.

39 Arya S, Nair D, Chellani H, Deb M, Hasan AS, Jawa G, et al. Molecular evidence suggestive of intrauterine transmission of *Neisseria meningitidis* serogroup A from mother to infant. *J Pediatr Infect Dis* 2007;2:45–50.

40 Selander B, Schliamser S, Schalen C, Fredlund H, Unemo M, Johansson PJ. A premature infant with fulminant meningococcal septicaemia. *Scand J Infect Dis* 2003;35:345–8.

41 Cigni A, Cossellu S, Porcu A, Piga S. Meningococcal osteomyelitis in a premature infant. *Ann Ital Med Int* 2004;19:280–2.

42 Ellis M, Weindling AM, Davidson DC, Ho N, Damjanovic V. Neonatal meningococcal conjunctivitis associated with meningococcal meningitis. *Arch Dis Child* 1992;67(10 Spec No):1219–20.

43 Dinakaran S, Desai SP. Group-C meningococcal conjunctivitis in a neonate. *Ocul Immunol Inflamm* 2000;8:123–5.

44 Tzeng YL, Bazan JA, Turner AN, Wang X, Retchless AC, Read TD, et al. Emergence of a new *Neisseria meningitidis* clonal complex 11 lineage 11.2 clade as an effective urogenital pathogen. *Proc Natl Acad Sci USA* 2017;114:4237–42.

Chapter Five

4. Discussion

These studies focus on the lead up to the introduction of 4CMenB into the national infant immunisation programme in September 2015 and the subsequent effect of the vaccine on the epidemiology of MenB disease. The epidemiology of IMD varies both regionally and over time, as different strains are introduced into the population and others abate naturally or through vaccination (Harrison et al., 2009). The epidemiology of IMD in England has been well documented and trends in disease have fluctuated due to both cyclical peaks and the implementation of successful vaccination programmes, namely the MCC programme that was implemented to combat an outbreak of MenC disease in the early 2000s (Miller et al., 2001). However, even during this MenC peak, MenB has been responsible for the majority of disease.

3.1. Epidemiology and predicting 4CMenB strain coverage prior to vaccine introduction in England

The studies in this chapter presented the epidemiology of overall IMD but focused on MenB cases in England along with the predicted strain coverage of the 4CMenB vaccine against circulating strains in England before it was included in the national infant immunisation programme. Study 1 established baseline trends in epidemiology, age distribution, clinical presentations and disease outcomes of IMD in England between 2011 and 2015. These findings showed that English epidemiology was similar to the rest of Europe, where the majority of IMD is caused by group B meningococci (ECDC, 2017b). The age distribution of IMD was also similar to that of other European (ECDC, 2017b) and North American countries (MacNeil et al., 2018). Study 1 was the first to report a low prevalence of known risk factors among IMD cases in England.

Study 2 presented MATS coverage estimates for 2014-15 MenB isolates in the UK and compared them with MATS coverage and regional distribution with corresponding 2007-

08 data. The study estimated the coverage of the vaccine as well as stratifying these estimates by age group, geographical region, disease severity and outcome. While the number of MenB cases in 2014-15 was nearly half of that in 2007-08, this study showed MATS coverage declined by 7% and the number of isolates covered by more than one antigen dropped by 15% (Parikh et al., 2017). These findings seem to be at odds with evidence using human SBA (hSBA) data of 4CMenB-vaccinated adolescents which reported that a third had no bactericidal antibodies against the outbreak strain, even though this strain was predicted by MATS to be covered on fHbp and NHBA components (Basta et al., 2016). It is widely acknowledged that MATS results should be treated with caution as is thought to be a conservative estimate when compared to serum bactericidal antibodies (SBA) (Frosi et al., 2013).This is because small amounts of antibody against a few antigens can act synergistically (Giuliani et al., 2010). Furthermore, estimates of vaccine antigen coverage, as based on the measurement of antigen in antibody binding assays are designed to quantify the antigen expressed by the meningococcal isolate rather than directly measuring the antibody response of the vaccinated individual (Feavers and Maiden, 2017).

The findings in Study 2 showed that the year before the introduction of 4CMenB, a third of circulating MenB strains in the UK would not be covered by the vaccine. This aligned with results from another study using the Bexsero Antigen Sequence Type (BAST) scheme, a genotype-phenotype modelling system, which also predicted 66% coverage for MenB isolates in the UK and Ireland between 2010-14 (Brehony et al., 2016). However, using clonal complex as a proxy for predicting MATS positivity, as BAST does, has been shown to be unreliable, due to the dynamic antigen expression within strains, within clonal complexes or both (Vogel et al., 2013; Abad et al., 2016). A downfall of MATS and BAST methods are that they are limited by their requirement for isolates from culture-confirmed cases of IMD. This could be an ongoing problem as work has shown that only about half of all confirmed cases, across all age groups, in England are confirmed by culture (Parikh et al., 2018). As a potential way to increase the amount of samples to estimate 4CMenB strain coverage, Muzzi and colleagues (2019) recently used antigen genotyping to complement MATS (gMATS) which is a

purely genetic approach and thus can be performed on non-culture specimens as well. The gMATS method found a predicted coverage of 72-73% in England and Wales, which underestimated hSBA estimates (Frosi et al., 2013) and the first VE estimates for England (Parikh et al., 2016) but is higher than later VE estimates in England (Ladhani et al., 2020).

The potential of 4CMenB to protect against MenW disease has been shown (Ladhani et al., 2016). Study 3 explored the potential number of infant MenW cases that could be averted through the national 4CMenB vaccination campaign. The second highest burden of IMD cases in infants in England is caused by MenW (Ladhani et al., 2015; Parikh et al., 2018). Study 3 suggested that a large number of cases may be averted in infants as the vaccine has been shown to elicit antibodies against the MenW: cc11 causing most disease in this age group. The real-world estimates on VE and impact on MenW disease in England are currently being undertaken.

3.2. Estimates on the effectiveness and impact of the 4CMenB vaccine in England

Impact and effectiveness of 4CMenB has been shown elsewhere. During a local outbreak of MenB disease in Quebec, Canada in 2014, 82% of 59,000 eligible individuals aged two months to 20 years of age were immunized, no cases of IMD arose in vaccinated persons and their analysis showed a 78% reduction in IMD after this vaccination campaign (Flacco et al., 2018). 4CMenB has been used in multiple university outbreaks, in thousands of adolescents, yet none have reported additional cases (McNamara et al., 2015; Basta et al., 2016; Biswas, 2016; Duffy et al., 2017; Thabuis et al., 2018).

The studies in this chapter were the first to show a reduced two-dose infant priming schedule of the 4CMenB vaccine was effective in preventing MenB disease in infants aged younger than 12 months and showed that cases of MenB halved in vaccine eligible infants during the first 10 months of the programme in England. These findings were used to support the introduction of 4CMenB in other countries (ECDC, 2017a) and

will provide evidence for updating the vaccine's licensure from a three dose to a two-dose priming schedule. These studies also provided the first real-world evidence of the effectiveness of 4CMenB in preventing MenB disease 3 years after its introduction into the U.K national infant immunisation programme and showed that the 12-month booster protected against MenB disease for at least 2 years, which was reassuring given the initial concerns about rapidly waning levels of antibodies (Martin and Snape, 2013). These findings are particularly important as the highest burden of MenB disease in England is before three years of age (Ladhani et al., 2016).

3.3. Epidemiology of IMD in vulnerable populations

Study 5 demonstrated the first 4CMenB vaccine failure in a young adult on long-term terminal complement inhibitor therapy, Eculizumab. An unwanted complication of this therapy is an increased risk of infection with encapsulated bacteria, particularly *Neisseria meningitidis* (Nester and Thomas, 2012). Although individuals with complement deficiency are at an increased risk, it seems they generally experience less severe disease with low case fatality (Figueroa and Densen, 1991). One explanation suggests there may be a lower release of endotoxin from the bacterial surface when a terminal complement pathway is not intact (Figueroa and Densen, 1991). However, more recent research showed that while Eculizumab inhibits bactericidal activity via complement-mediated serum, it does not block opsonophagocytic activity, which does not require the terminal complement pathway to function and thus this may help prevent severe disease (Findlow et al., 2015). There is also potential hope in a new drug (ACH-4471) that may be able to be used in place of Eculizumab that carries less of a risk of developing IMD in patients on this treatment (Ellis-Pegler et al., 2016). Other work has since been published that aligns with the findings in Study 5 and describes patients with inherited and acquired complement deficiency who developed IMD in England over a decade. It showed that in England, complement deficiency is rare among IMD cases, these findings included inherited disorders of the late complement pathway, immune-mediated disorders associated with low complement levels and patients on Eculizumab therapy (Ladhani et al., 2019).

Study 7 looked at another group at an increased risk for invasive disease, those who initially present with primary meningococcal conjunctivitis (PMC). It was well documented that those initially presenting with PMC are at an increased risk of developing systemic disease. This study showed a clear gap in consistent clinical recommendations for the treatment of these cases while confirming that current UK public health guidelines on the management of these cases is rooted in firm evidence. A recent study also identified resistant meningococcal conjunctivitis in people returning from Mecca (Zumla and Memish, 2019), which provides additional evidence for highlighting the urgent need to review currently recommended prophylactic measures, maybe particularly for Hajj pilgrims, in an effort to best prevent cases of systemic IMD.

Study 8 showed, for the first time, the unusual finding of a decreased risk of IMD amongst pregnant women when compared to non-pregnant women of a comparable age. Pregnancy is often considered a general condition of immunosuppression and other studies have shown pregnant women to be at an increased risk for a number of other bacterial infections including non-typeable *Haemophilus influenzae* (ntHi) disease (Collins et al., 2014) listeriosis (Mylonakis et al., 2002; Goulet et al., 2012; Pouillot et al., 2012) and invasive group B streptococcus (GBS) disease (Deutscher et al., 2011). This increased risk has been thought to be related to the placental immune response and its tropism for specific pathogens that are suspected to affect the pregnant woman's susceptibility to and severity of certain infectious diseases (Mor and Cardenas, 2010). A possible reason of why pregnant women may be at a lower risk for IMD may be due to changes in their social interaction with others, resulting in lower exposure to meningococcal carriers (Parikh et al., 2019). Study 8 and the included reviewed literature still showed that if contracted during pregnancy, IMD can still be a severe infection and additionally clinicians should still be aware of the ability of meningococci to colonize the urogenital and anal tracts (Sunderland et al., 1972; Givan et al., 1977) (Givan et al, 1977; Sunderland et al, 1972) which is then still poses a risk of transmission during sexual contact and childbirth. A very recent study showed commensal *Neisseria* can be shared between intimate partners, this could have

implications for both antimicrobial resistance and an increase in sexual transmission of meningococci over time but will require more insight.

5. Conclusions

This collection of studies has shown the importance and impact of the 4CMenB vaccine on the epidemiology of MenB disease in England. The multidisciplinary surveillance system in England allowed for the collection of high-quality national data which was used to generate information on IMD case numbers, disease characteristics, estimate the impact and effectiveness of 4CMenB in vaccinated populations in England and identify vaccine failures. These studies established both epidemiological and molecular baselines of MenB disease prior to the introduction of 4CMenB in late 2015. The two studies on the impact and effectiveness at 10 months and three years post introduction were the first to show sustained impact on MenB disease and real-world vaccine effectiveness. Furthermore, this work highlighted the need for increased awareness in health professionals responsible for the care of complement deficient patients and potential failure to illicit immune responses to 4CMenB vaccine. These studies also identified gaps in clear clinical recommendations in the treatment of individuals with primary meningococcal conjunctivitis, who are at an increased risk for systemic disease. Finally, this work was the first to attribute a decreased risk of IMD in pregnant women in England.

6. Future work

As genomic analyses of meningococci are a routine component of enhanced national surveillance data in England, there is a breadth of information available on isolates of IMD. However, it is still not fully understood why disease presentation and severity varies so widely from person to person, thus there is a need for genome comparison studies between human and bacterial genomes, in an effort to elucidate potential explanations for these variations and use these potential findings to better tailor recommendations and prophylactic efforts to protect those at an increased risk for severe disease. In 2019, an amendment was made to the enhanced national

surveillance protocol to encompass the retrospective collection of information on IMD outcomes and sequelae in children aged less than five years (from 01 September 2015 to present). This information provides the possibility to compare disease outcomes and recorded sequelae in vaccinated and unvaccinated children to understand if the vaccine is providing protection against severe disease. Currently, there are no recommendations for individuals with malignancies to receive vaccination as part of a risk group. Data from epidemiological questionnaires completed by local health protection teams also provides a potential to explore risk amongst individuals with reported malignancies and/or on immunosuppressive treatments. There are also early data to suggest 4CMenB may cross-react and offer protection against infection with *Neisseria gonorrhoeae* (Régnier and Huels, 2014), a bacteria famously associated with antibiotic resistance, further studies into the vaccine's effectiveness and impact against this disease could provide huge benefits to nearly 98 million new cases of gonorrhea occurring annually .

In 2017, the European Medicines Agency (EMA) licensed rLP2086 (Trumenba), a fHbp vaccine for active immunisation to prevent MenB disease in individuals at least ten years of age. This vaccine is different to 4CMenB in that Trumenba contains a variant from each of the two identified subfamilies of the meningococcal surface protein fHbp . The protein, fHbp is expressed by the majority of invasive meningococci and in an extensive program of clinical trials in adolescents and young adults, it was demonstrated that a two-dose or three-dose series of Trumenba elicits a strong immune response against a range of MenB test strains selected to be representative of strains prevalent in Europe and the USA . Population based data is required to estimate the true effectiveness of the vaccine and as it is not licensed for use in children less than 10 years of age, the protection of infants will rely on the ability of Trumenba to interrupt transmission in adolescents and thus provide herd protection (Feavers and Maiden, 2017).

References

Abad, R., Medina, V., Stella, M., Boccadifuoco, G., Comanducci, M., Bambini, S., Muzzi, A. and Vázquez, J. A. (2016) 'Predicted Strain Coverage of a New Meningococcal Multicomponent Vaccine (4CMenB) in Spain: Analysis of the Differences with Other European Countries.' *PloS One*, 11(3) p. e0150721.

Ala'Aldeen, D. A. A., Neal, K. R., Ait-Tahar, K., Nguyen-Van-Tam, J. S., English, A., Falla, T. J., Hawkey, P. M. and Slack, R. C. B. (2000) 'Dynamics of Meningococcal Long-Term Carriage among University Students and Their Implications for Mass Vaccination.' *Journal of Clinical Microbiology*. American Society for Microbiology (ASM), 38(6) pp. 2311–2311.

Ali, A., Jafri, R. Z., Messonnier, N., Tevi-Benissan, C., Durrheim, D., Eskola, J., Fermon, F., Klugman, K. P., Ramsay, M., Sow, S., Zhujun, S., Bhutta, Z. and Abramson, J. (2014) 'Global practices of meningococcal vaccine use and impact on invasive disease.' *Pathogens and Global Health*, 108(1) pp. 11–20.

Arnold, R., Galloway, Y., McNicholas, A. and O'Hallahan, J. (2011) 'Effectiveness of a vaccination programme for an epidemic of meningococcal B in New Zealand.' *Vaccine*, 29(40) pp. 7100–7106.

Barquet, N., Gasser, I., Domingo, P., Moraga, F. A., Macaya, A. and Elcuaz, R. (1990) 'Primary meningococcal conjunctivitis: report of 21 patients and review.' *Reviews of Infectious Diseases*, 12(5) pp. 838–847.

Bart, A., Dankert, J. and van der Ende, A. (2000) 'Representational difference analysis of Neisseria meningitidis identifies sequences that are specific for the hyper-virulent lineage III clone.' *FEMS microbiology letters*, 188(2) pp. 111–114.

Basta, N. E., Mahmoud, A. A. F., Wolfson, J., Ploss, A., Heller, B. L., Hanna, S., Johnsen, P., Izzo, R., Grenfell, B. T., Findlow, J., Bai, X. and Borrow, R. (2016) 'Immunogenicity of a Meningococcal B Vaccine during a University Outbreak.' *The New England Journal of Medicine*, 375(3) pp. 220–228.

Biswas, H. H. (2016) 'Notes from the Field: Outbreak of Serogroup B Meningococcal Disease at a University — California, 2016.' *MMWR. Morbidity and Mortality Weekly Report*, 65.

Booy, R., Gentile, A., Nissen, M., Whelan, J. and Abitbol, V. (2018) 'Recent changes in the epidemiology of Neisseria meningitidis serogroup W across the world, current vaccination policy choices and possible future strategies.' *Human Vaccines & Immunotherapeutics*, 15(2) pp. 470–480.

Borrow, R., Alarcón, P., Carlos, J., Caugant, D. A., Christensen, H., Debbag, R., De Wals, P., Echániz-Aviles, G., Findlow, J., Head, C., Holt, D., Kamiya, H., Saha, S. K., Sidorenko, S., Taha, M. K., Trotter, C., Vázquez Moreno, J. A., von Gottberg, A. and Sáfadi, M. A. P. (2017) 'The Global Meningococcal Initiative: global epidemiology, the

impact of vaccines on meningococcal disease and the importance of herd protection.' *Expert Review of Vaccines*. Taylor and Francis Ltd, 16(4) pp. 313–328.

Brehony, C., Rodrigues, C. M. C., Borrow, R., Smith, A., Cunney, R., Moxon, E. R. and Maiden, M. C. J. (2016) 'Distribution of Bexsero® Antigen Sequence Types (BASTs) in invasive meningococcal disease isolates: Implications for immunisation.' *Vaccine*, 34(39) pp. 4690–4697.

Campbell, H., Saliba, V., Borrow, R., Ramsay, M. and Ladhani, S. N. (2015) 'Targeted vaccination of teenagers following continued rapid endemic expansion of a single meningococcal group W clone (sequence type 11 clonal complex), United Kingdom 2015.' *Eurosurveillance*. European Centre for Disease Prevention and Control (ECDC), 20(28).

Cartwright, K. A., Jones, D. M., Smith, A. J., Stuart, J. M., Kaczmarski, E. B. and Palmer, S. R. (1991) 'Influenza A and meningococcal disease.' *Lancet (London, England)*, 338(8766) pp. 554–557.

Caugant, D. A. and Maiden, M. C. J. (2009) 'Meningococcal carriage and disease-Population biology and evolution.' *Vaccine*. Elsevier, 27(SUPPL. 2) pp. B64–B64.

Collins, S., Ramsay, M., Slack, M. P. E., Campbell, H., Flynn, S., Litt, D. and Ladhani, S. N. (2014) 'Risk of invasive Haemophilus influenzae infection during pregnancy and association with adverse fetal outcomes.' *JAMA*, 311(11) pp. 1125–1132.

Corless, C. E., Guiver, M., Borrow, R., Edwards-Jones, V., Fox, A. J. and Kaczmarski, E. B. (2001) 'Simultaneous detection of Neisseria meningitidis, Haemophilus influenzae, and Streptococcus pneumoniae in suspected cases of meningitis and septicemia using real-time PCR.' *Journal of Clinical Microbiology*, 39(4) pp. 1553–1558.

Davila, S., Wright, V. J., Khor, C. C., Sim, K. S., Binder, A., Breunis, W. B., Inwald, D., Nadel, S., Betts, H., Carrol, E. D., de Groot, R., Hermans, P. W. M., Hazelzet, J., Emonts, M., Lim, C. C., Kuijpers, T. W., Martinon-Torres, F., Salas, A., Zenz, W., Levin, M., Hibberd, M. L. and International Meningococcal Genetics Consortium (2010) 'Genome-wide association study identifies variants in the CFH region associated with host susceptibility to meningococcal disease.' *Nature Genetics*, 42(9) pp. 772–776.

Deutscher, M., Lewis, M., Zell, E. R., Taylor, T. H., Van Beneden, C., Schrag, S. and Active Bacterial Core Surveillance Team (2011) 'Incidence and severity of invasive Streptococcus pneumoniae, group A Streptococcus, and group B Streptococcus infections among pregnant and postpartum women.' *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, 53(2) pp. 114–123.

Domingo, P., Muñiz-Diaz, E., Baraldès, M. A., Arilla, M., Barquet, N., Pericas, R., Juárez, C., Madoz, P. and Vázquez, G. (2002) 'Associations between Fc gamma receptor IIA polymorphisms and the risk and prognosis of meningococcal disease.' *The American Journal of Medicine*, 112(1) pp. 19–25.

Domnich, A., Gasparini, R., Amicizia, D., Boccadifuoco, G., Giuliani, M. M. and Panatto, D. (2015) 'Meningococcal Antigen Typing System Development and Application to the Evaluation of Effectiveness of Meningococcal B Vaccine and Possible Use for Other Purposes.' *Journal of Immunology Research*, 2015 p. 353461.

Donnelly, J., Medini, D., Boccadifuoco, G., Biolchi, A., Ward, J., Frasch, C., Moxon, E. R., Stella, M., Comanducci, M., Bambini, S., Muzzi, A., Andrews, W., Chen, J., Santos, G., Santini, L., Boucher, P., Serruto, D., Pizza, M., Rappuoli, R. and Giuliani, M. M. (2010) 'Qualitative and quantitative assessment of meningococcal antigens to evaluate the potential strain coverage of protein-based vaccines.' *Proceedings of the National Academy of Sciences of the United States of America*, 107(45) pp. 19490–19495.

Duffy, J., Johnsen, P., Ferris, M., Miller, M., Leighton, K., McGilvray, M., McNamara, L., Breakwell, L., Yu, Y., Bhavsar, T., Briere, E. and Patel, M. (2017) 'Safety of a meningococcal group B vaccine used in response to two university outbreaks.' *Journal of American college health : J of ACH*, 65(6) pp. 380–388.

ECDC (2017a) 'Expert opinion on the introduction of the meningococcal B (4CMenB) vaccine in the EU/EEA' p. 38.

ECDC (2017b) *Invasive meningococcal disease Annual Epidemiological Report for 2017 Key facts*.

Ellis, M., Weindling, A. M., Davidson, D. C., Ho, N. and Damjanovic, V. (1992) 'Neonatal meningococcal conjunctivitis associated with meningococcal meningitis.' *Archives of Disease in Childhood*, 67(10 Spec No) pp. 1219–1220.

Ellis-Pegler, R., Schwabe, C., Ajari, I., Robinson, H., Sorensen, R., Lahey, J., Yang, W., Huang, M., Hui, J., Kocinsky, H., Geffner, H. and Apelian, D. (2016) 'An Orally Administered Small Molecule Factor D Inhibitor (ACH-4471) For Treatment of PNH, C3G and Complement-Mediated Diseases:Interim Phase 1 Results in Healthy Volunteers.' *In*. Copenhagen, Denmark.

Farrington, C. P. (1993) 'Estimation of vaccine effectiveness using the screening method.' *International Journal of Epidemiology*, 22(4) pp. 742–746.

Feavers, I. M. and Maiden, M. C. J. (2017) 'Recent Progress in the Prevention of Serogroup B Meningococcal Disease.' *Clinical and vaccine immunology: CVI*, 24(5).

Figueroa, J., Andreoni, J. and Densen, P. (1993) 'Complement deficiency states and meningococcal disease.' *Immunologic Research*, 12(3) pp. 295–311.

Figueroa, J. E. and Densen, P. (1991) 'Infectious diseases associated with complement deficiencies.' *Clinical Microbiology Reviews*, 4(3) pp. 359–395.

Findlow, J., Bai, X. and Carr, D. (2015) 'Effect of Eculizumab (Solaris), on the Meningococcal Serogroup B Serum Bactericidal Antibody Activity and Opsonophagocytic Activity.' *In*. Amsterdam, Netherlands.

Flacco, M. E., Manzoli, L., Rosso, A., Marzuillo, C., Bergamini, M., Stefanati, A., Cultrera, R., Villari, P., Ricciardi, W., Ioannidis, J. P. A. and Contopoulos-Ioannidis, D. G. (2018) 'Immunogenicity and safety of the multicomponent meningococcal B vaccine (4CMenB) in children and adolescents: a systematic review and meta-analysis.' *The Lancet. Infectious Diseases*, 18(4) pp. 461–472.

Flexner, S. (1913) 'THE RESULTS OF THE SERUM TREATMENT IN THIRTEEN HUNDRED CASES OF EPIDEMIC MENINGITIS.' *The Journal of Experimental Medicine*, 17(5) pp. 553–576.

Frosi, G., Biolchi, A., Lo Sapio, M., Rigat, F., Gilchrist, S., Lucidarme, J., Findlow, J., Borrow, R., Pizza, M., Giuliani, M. M. and Medini, D. (2013) 'Bactericidal antibody against a representative epidemiological meningococcal serogroup B panel confirms that MATS underestimates 4CMenB vaccine strain coverage.' *Vaccine*, 31(43) pp. 4968–4974.

Giuliani, M. M., Biolchi, A., Serruto, D., Ferlicca, F., Vienken, K., Oster, P., Rappuoli, R., Pizza, M. and Donnelly, J. (2010) 'Measuring antigen-specific bactericidal responses to a multicomponent vaccine against serogroup B meningococcus.' *Vaccine*, 28(31) pp. 5023–5030.

Givan, K. F., Thomas, B. W. and Johnston, A. G. (1977) 'Isolation of Neisseria meningitidis from the urethra, cervix, and anal canal: further observations.' *British Journal of Venereal Diseases*, 53(2) pp. 109–112.

Goulet, V., Hebert, M., Hedberg, C., Laurent, E., Vaillant, V., De Valk, H. and Desenclos, J.-C. (2012) 'Incidence of listeriosis and related mortality among groups at risk of acquiring listeriosis.' *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, 54(5) pp. 652–660.

Gray, S. J., Trotter, C. L., Ramsay, M. E., Guiver, M., Fox, A. J., Borrow, R., Mallard, R. H. and Kaczmarski, E. B. (2006) 'Epidemiology of meningococcal disease in England and Wales 1993/94 to 2003/04: Contribution and experiences of the Meningococcal Reference Unit.' *Journal of Medical Microbiology*. Microbiology Society, 55(7) pp. 887–896.

Harfi, H. A., Stapleton, F. B., Nazer, H., Oh, W. and Whitley, R. J. (2012) *Textbook of Clinical Pediatrics*. Springer Science & Business Media.

Harrison, L. H., Trotter, C. L. and Ramsay, M. E. (2009) 'Global epidemiology of meningococcal disease.' *Vaccine*, 27 Suppl 2, June, pp. B51-63.

Holst, J., Martin, D., Arnold, R., Huergo, C. C., Oster, P., O'Hallahan, J. and Rosenqvist, E. (2009) 'Properties and clinical performance of vaccines containing outer membrane vesicles from Neisseria meningitidis.' *Vaccine*, 27 Suppl 2, June, pp. B3-12.

Jacobs, J. H., Viboud, C., Tchetgen, E. T., Schwartz, J., Steiner, C., Simonsen, L. and Lipsitch, M. (2014) 'The Association of Meningococcal Disease with Influenza in the United States, 1989–2009.' *PLoS ONE*, 9(9).

Jódar, L., Feavers, I. M., Salisbury, D. and Granoff, D. M. (2002) 'Development of vaccines against meningococcal disease.' *Lancet (London, England)*, 359(9316) pp. 1499–1508.

Jolley, K. A., Hill, D. M. C., Bratcher, H. B., Harrison, O. B., Feavers, I. M., Parkhill, J. and Maiden, M. C. J. (2012) 'Resolution of a Meningococcal Disease Outbreak from Whole-Genome Sequence Data with Rapid Web-Based Analysis Methods.' *Journal of Clinical Microbiology*, 50(9) pp. 3046–3053.

Kanai, M., Kamiya, H., Smith-Palmer, A., Takahashi, H., Hachisu, Y., Fukusumi, M., Saitoh, T., Ohnishi, M., Sunagawa, T., Matsui, T. and Oishi, K. (2017) 'Meningococcal disease outbreak related to the World Scout Jamboree in Japan, 2015.' *Western Pacific Surveillance and Response Journal : WPSAR*, 8(2) pp. 25–30.

Kuehn, M. J. and Kesty, N. C. (2005) 'Bacterial outer membrane vesicles and the host-pathogen interaction.' *Genes & Development*, 19(22) pp. 2645–2655.

Kugelberg, E., Gollan, B. and Tang, C. M. (2008) 'Mechanisms in Neisseria meningitidis for resistance against complement-mediated killing.' *Vaccine*. Elsevier, 26(SUPPL. 8) p. I34.

Ladhani, S. N., Andrews, N., Parikh, S. R., Campbell, H., White, J., Edelstein, M., Bai, X., Lucidarme, J., Borrow, R. and Ramsay, M. E. (2020) 'Vaccination of Infants with Meningococcal Group B Vaccine (4CMenB) in England.' *New England Journal of Medicine*. Massachusetts Medical Society, 382(4) pp. 309–317.

Ladhani, S. N., Beebeejaun, K., Lucidarme, J., Campbell, H., Gray, S., Kaczmarski, E., Ramsay, M. E. and Borrow, R. (2015) 'Increase in endemic Neisseria meningitidis capsular group W sequence type 11 complex associated with severe invasive disease in England and Wales.' *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, 60(4) pp. 578–585.

Ladhani, S. N., Campbell, H., Lucidarme, J., Gray, S., Parikh, S., Willerton, L., Clark, S. A., Lekshmi, A., Walker, A., Patel, S., Bai, X., Ramsay, M. and Borrow, R. (2019) 'Invasive meningococcal disease in patients with complement deficiencies: a case series (2008-2017).' *BMC infectious diseases*, 19(1) p. 522.

Ladhani, S. N., Flood, J. S., Ramsay, M. E., Campbell, H., Gray, S. J., Kaczmarski, E. B., Mallard, R. H., Guiver, M., Newbold, L. S. and Borrow, R. (2012) 'Invasive meningococcal disease in England and Wales: Implications for the introduction of new vaccines.' *Vaccine*. Elsevier, 30(24) pp. 3710–3716.

Ladhani, S. N., Giuliani, M. M., Biolchi, A., Pizza, M., Beebeejaun, K., Lucidarme, J., Findlow, J., Ramsay, M. E. and Borrow, R. (2016) 'Effectiveness of Meningococcal B

Vaccine against Endemic Hypervirulent Neisseria meningitidis W Strain, England.' *Emerging Infectious Diseases*, 22(2) pp. 309–311.

Latex agglutination test: MedlinePlus Medical Encyclopedia (n.d.). [Online] [Accessed on 17th March 2020] https://medlineplus.gov/ency/article/003334.htm.

Lewis, L. A. and Ram, S. (2014) 'Meningococcal disease and the complement system.' *Virulence*, 5(1) pp. 98–126.

Lucas, M., Brouwer, M. and Beek, D. (2016) 'Neurological sequelae of bacterial meningitis.' *The Journal of infection*, 73, April.

Lucidarme, J., Hill, D. M. C., Bratcher, H. B., Gray, S. J., du Plessis, M., Tsang, R. S. W., Vazquez, J. A., Taha, M.-K., Ceyhan, M., Efron, A. M., Gorla, M. C., Findlow, J., Jolley, K. A., Maiden, M. C. J. and Borrow, R. (2015) 'Genomic resolution of an aggressive, widespread, diverse and expanding meningococcal serogroup B, C and W lineage.' *The Journal of Infection*, 71(5) pp. 544–552.

Lucidarme, J., Lekshmi, A., Parikh, S. R., Bray, J. E., Hill, D. M., Bratcher, H. B., Gray, S. J., Carr, A. D., Jolley, K. A., Findlow, J., Campbell, H., Ladhani, S. N., Ramsay, M. E., Maiden, M. C. J. and Borrow, R. (2017) 'Frequent capsule switching in "ultra-virulent" meningococci – Are we ready for a serogroup B ST-11 complex outbreak?' *Journal of Infection*. W.B. Saunders Ltd, 75(2) pp. 95–103.

MacNeil, J. R., Blain, A. E., Wang, X. and Cohn, A. C. (2018) 'Current Epidemiology and Trends in Meningococcal Disease-United States, 1996-2015.' *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, 66(8) pp. 1276–1281.

Madico, G., Welsch, J. A., Lewis, L. A., McNaughton, A., Perlman, D. H., Costello, C. E., Ngampasutadol, J., Vogel, U., Granoff, D. M. and Ram, S. (2006) 'The meningococcal vaccine candidate GNA1870 binds the complement regulatory protein factor H and enhances serum resistance.' *Journal of Immunology (Baltimore, Md.: 1950)*, 177(1) pp. 501–510.

Maiden, M. C., Bygraves, J. A., Feil, E., Morelli, G., Russell, J. E., Urwin, R., Zhang, Q., Zhou, J., Zurth, K., Caugant, D. A., Feavers, I. M., Achtman, M. and Spratt, B. G. (1998) 'Multilocus sequence typing: a portable approach to the identification of clones within populations of pathogenic microorganisms.' *Proceedings of the National Academy of Sciences of the United States of America*, 95(6) pp. 3140–3145.

Mandal, S., Campbell, H., Ribeiro, S., Gray, S., Carr, T., White, J., Ladhani, S. N. and Ramsay, M. E. (2017) 'Risk of invasive meningococcal disease in university students in England and optimal strategies for protection using MenACWY vaccine.' *Vaccine*, 35(43) pp. 5814–5818.

Martin, N. G. and Snape, M. D. (2013) 'A multicomponent serogroup B meningococcal vaccine is licensed for use in Europe: what do we know, and what are we yet to learn?' *Expert Review of Vaccines*, 12(8) pp. 837–858.

Martinón-Torres, F., Png, E., Khor, C. C., Davila, S., Wright, V. J., Sim, K. S., Vega, A., Fachal, L., Inwald, D., Nadel, S., Carrol, E. D., Martinón-Torres, N., Alonso, S. M., Carracedo, A., Morteruel, E., López-Bayón, J., Torre, A. C., Monge, C. C., Aguilar, P. A. G. de, Torné, E. E., Martínez-Padilla, M. del C., Martinón-Sánchez, J. M., Levin, M., Hibberd, M. L., Salas, A., Gómez-Carballa, A., Cebey, M., Sánchez, N. G., Calle, I. R., Grande, A. J., Pardo-Seco, J., Barral-Arca, R., Pischedda, S., Currás-Tuala, M.-J., Rodriguez-Tenreiro, C., Redondo-Collazo, L., Sánchez, F. P., Moreno, J. de la C., Miralles, M. L. M., Rodríguez, J. L. G., García, S. R., Doce, A. H., Barba, Á. F., Pallares, M. O., Romero, A. R., Bonet, J. I. M., Cancela, M. S., Bergara, E. O., Arriortua, A. B., Gómez, M. L. N., Fernández, M. S., Martínez, X. A., Ortega, Á. C., Rosso, S. P., Macarrón, C. P. C., Menchón, N. M., Sánchez, F. G., Garzón, M. G.-R., García, M. del M. B., Granados, J. M. S., Ayestarán, O. S., Payo, R., Palazón, S. C., León, M. C. L., Dominguez, S. R., Villanueba, D. A., Martín, J. A. A., Orayen, C. G., Iturbe, E. B., Salas, M. T. A., Fernández, I. Q., Booy, R., Coin, L. J. M., Eleftherohorinou, H., Faust, S., Galassini, R., Habibi, P., Haralambous, E., Kroll, S., Langford, P., Pathan, N., Pollard, A. J., Abdulla, F., Agapow, P., Bellos, E., Hamilton, S., Herberg, J. A., Hoggart, C., Kaforou, M., Mashbat, M., Mustafa, S. and Sancho-Shimizu, V. (2016) 'Natural resistance to Meningococcal Disease related to CFH loci: Meta-analysis of genome-wide association studies.' *Scientific Reports*. Nature Publishing Group, 6(1) pp. 1–9.

McNamara, L. A., Shumate, A. M., Johnsen, P., MacNeil, J. R., Patel, M., Bhavsar, T., Cohn, A. C., Dinitz-Sklar, J., Duffy, J., Finnie, J., Garon, D., Hary, R., Hu, F., Kamiya, H., Kim, H.-J., Kolligian, J., Neglia, J., Oakley, J., Wagner, J., Wagner, K., Wang, X., Yu, Y., Montana, B., Tan, C., Izzo, R. and Clark, T. A. (2015) 'First Use of a Serogroup B Meningococcal Vaccine in the US in Response to a University Outbreak.' *Pediatrics*, 135(5) pp. 798–804.

Miller, E., Salisbury, D. and Ramsay, M. (2001) 'Planning, registration, and implementation of an immunisation campaign against meningococcal serogroup C disease in the UK: a success story.' *Vaccine*, 20 Suppl 1, October, pp. S58-67.

Mond, J. J., Lees, A. and Snapper, C. M. (1995) 'T cell-independent antigens type 2.' *Annual Review of Immunology*, 13 pp. 655–692.

Mor, G. and Cardenas, I. (2010) 'The Immune System in Pregnancy: A Unique Complexity.' *American journal of reproductive immunology (New York, N.Y. : 1989)*, 63(6) pp. 425–433.

de Moraes, J. C., Perkins, B. A., Camargo, M. C., Hidalgo, N. T., Barbosa, H. A., Sacchi, C. T., Landgraf, I. M., Gattas, V. L., Vasconcelos, H. de G. and Gral, I. M. (1992) 'Protective efficacy of a serogroup B meningococcal vaccine in Sao Paulo, Brazil.' *Lancet (London, England)*, 340(8827) pp. 1074–1078.

Muzzi, A., Brozzi, A., Serino, L., Bodini, M., Abad, R., Caugant, D., Comanducci, M., Lemos, A. P., Gorla, M. C., Křížová, P., Mikula, C., Mulhall, R., Nissen, M., Nohynek, H., Simões, M. J., Skoczyńska, A., Stefanelli, P., Taha, M.-K., Toropainen, M., Tzanakaki, G., Vadivelu-Pechai, K., Watson, P., Vazquez, J. A., Rajam, G., Rappuoli, R., Borrow, R. and Medini, D. (2019) 'Genetic Meningococcal Antigen Typing System (gMATS): A genotyping tool that predicts 4CMenB strain coverage worldwide.' *Vaccine*, 37(7) pp. 991–1000.

Mylonakis, E., Paliou, M., Hohmann, E. L., Calderwood, S. B. and Wing, E. J. (2002) 'Listeriosis during pregnancy: a case series and review of 222 cases.' *Medicine*, 81(4) pp. 260–269.

Nester, C. M. and Thomas, C. P. (2012) 'Atypical hemolytic uremic syndrome: what is it, how is it diagnosed, and how is it treated?' *Hematology. American Society of Hematology. Education Program*, 2012 pp. 617–625.

Newton, D. A. and Wilson, W. G. (1977) 'Primary meningococcal conjunctivitis.' *Pediatrics*, 60(1) pp. 104–106.

Odegaard, A. (1983) 'Primary meningococcal conjunctivitis followed by meningitis and septicemia.' *NIPH annals*, 6(1) pp. 55–57.

Olea, A., Matute, I., González, C., Delgado, I., Poffald, L., Pedroni, E., Alfaro, T., Hirmas, M., Nájera, M., Gormaz, A., López, D., Loayza, S., Ferreccio, C., Gallegos, D., Fuentes, R., Vial, P. and Aguilera, X. (2017) 'Case−Control Study of Risk Factors for Meningococcal Disease in Chile.' *Emerging Infectious Diseases*, 23(7) pp. 1070–1078.

Palmgren, H. (2009) 'Meningococcal disease and climate.' *Global Health Action*, 2, November.

Parikh, S. R., Andrews, N. J., Beebeejaun, K., Campbell, H., Ribeiro, S., Ward, C., White, J. M., Borrow, R., Ramsay, M. E. and Ladhani, S. N. (2016) 'Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in England: a national observational cohort study.' *Lancet (London, England)*, 388(10061) pp. 2775–2782.

Parikh, S. R., Borrow, R., Ramsay, M. E. and Ladhani, S. N. (2019) 'Lower risk of invasive meningococcal disease during pregnancy: national prospective surveillance in England, 2011-2014.' *BJOG: an international journal of obstetrics and gynaecology*, 126(8) pp. 1052–1057.

Parikh, S. R., Campbell, H., Gray, S. J., Beebeejaun, K., Ribeiro, S., Borrow, R., Ramsay, M. E. and Ladhani, S. N. (2018) 'Epidemiology, clinical presentation, risk factors, intensive care admission and outcomes of invasive meningococcal disease in England, 2010–2015.' *Vaccine*. Elsevier Ltd, 36(26) pp. 3876–3881.

Parikh, S. R., Newbold, L., Slater, S., Stella, M., Moschioni, M., Lucidarme, J., De Paola, R., Giuliani, M., Serino, L., Gray, S. J., Clark, S. A., Findlow, J., Pizza, M.,

Ramsay, M. E., Ladhani, S. N. and Borrow, R. (2017) 'Meningococcal serogroup B strain coverage of the multicomponent 4CMenB vaccine with corresponding regional distribution and clinical characteristics in England, Wales, and Northern Ireland, 2007–08 and 2014–15: a qualitative and quantitative assessment.' *The Lancet Infectious Diseases*. Lancet Publishing Group, 17(7) pp. 754–762.

Patel, J. C., George, J., Vuong, J., Potts, C. C., Bozio, C., Clark, T. A., Thomas, J., Schier, J., Chang, A., Waller, J. L., Diaz, M. H., Whaley, M., Jenkins, L. T., Fuller, S., Williams, D. E., Redd, J. T., Arthur, R. R., Taweh, F., Vera Walker, Y., Hardy, P., Freeman, M., Katawera, V., Gwesa, G., Gbanya, M. Z., Clement, P., Kohar, H., Stone, M., Fallah, M., Nyenswah, T., Winchell, J. M., Wang, X., McNamara, L. A., Dokubo, E. K. and Fox, L. M. (2017) 'Rapid Laboratory Identification of Neisseria meningitidis Serogroup C as the Cause of an Outbreak - Liberia, 2017.' *MMWR. Morbidity and mortality weekly report*, 66(42) pp. 1144–1147.

Pizza, M. and Rappuoli, R. (2015) 'Neisseria meningitidis: Pathogenesis and immunity.' *Current Opinion in Microbiology*. Elsevier Ltd pp. 68–72.

Plikaytis, B. D., Stella, M., Boccadifuoco, G., DeTora, L. M., Agnusdei, M., Santini, L., Brunelli, B., Orlandi, L., Simmini, I., Giuliani, M., Ledroit, M., Hong, E., Taha, M.-K., Ellie, K., Rajam, G., Carlone, G. M., Claus, H., Vogel, U., Borrow, R., Findlow, J., Gilchrist, S., Stefanelli, P., Fazio, C., Carannante, A., Oksnes, J., Fritzsønn, E., Klem, A.-M., Caugant, D. A., Abad, R., Vázquez, J. A., Rappuoli, R., Pizza, M., Donnelly, J. J. and Medini, D. (2012) 'Interlaboratory standardization of the sandwich enzyme-linked immunosorbent assay designed for MATS, a rapid, reproducible method for estimating the strain coverage of investigational vaccines.' *Clinical and vaccine immunology: CVI*, 19(10) pp. 1609–1617.

Pouillot, R., Hoelzer, K., Jackson, K. A., Henao, O. L. and Silk, B. J. (2012) 'Relative risk of listeriosis in Foodborne Diseases Active Surveillance Network (FoodNet) sites according to age, pregnancy, and ethnicity.' *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, 54 Suppl 5, June, pp. S405-410.

Reese, F. M. (1936) 'Meningococcus Conjunctivitis Followed by Septicemia and Beginning Meningitis: A Case Report.' *American Journal of Ophthalmology*, 19(9) pp. 780–782.

Rosain, J., Hong, E., Fieschi, C., Martins, P. V., El Sissy, C., Deghmane, A.-E., Ouachée, M., Thomas, C., Launay, D., de Pontual, L., Suarez, F., Moshous, D., Picard, C., Taha, M.-K. and Frémeaux-Bacchi, V. (2017) 'Strains Responsible for Invasive Meningococcal Disease in Patients With Terminal Complement Pathway Deficiencies.' *The Journal of Infectious Diseases*, 215(8) pp. 1331–1338.

Rosenqvist, E., Høiby, E. A., Wedege, E., Bryn, K., Kolberg, J., Klem, A., Rønnild, E., Bjune, G. and Nøkleby, H. (1995) 'Human antibody responses to meningococcal outer

membrane antigens after three doses of the Norwegian group B meningococcal vaccine.' *Infection and Immunity*, 63(12) pp. 4642–4652.

Rouphael, N. G. and Stephens, D. S. (2012) 'Neisseria meningitidis: Biology, microbiology, and epidemiology.' *Methods in Molecular Biology*. NIH Public Access pp. 1–20.

Serruto, D., Spadafina, T., Ciucchi, L., Lewis, L. A., Ram, S., Tontini, M., Santini, L., Biolchi, A., Seib, K. L., Giuliani, M. M., Donnelly, J. J., Berti, F., Savino, S., Scarselli, M., Costantino, P., Kroll, J. S., O'Dwyer, C., Qiu, J., Plaut, A. G., Moxon, R., Rappuoli, R., Pizza, M. and Aricò, B. (2010) 'Neisseria meningitidis GNA2132, a heparin-binding protein that induces protective immunity in humans.' *Proceedings of the National Academy of Sciences of the United States of America*, 107(8) pp. 3770–3775.

Sierra, G. V. G., Campa, H. C., Varcacel, N. M., Garcia, I. L., Izquierdo, P. L., Sotolongo, P. F., Casanueva, G. V., Rico, C. O., Rodriguez, C. R. and Terry, M. H. (1991) 'Vaccine against group B Neisseia meningitidis: Protection trial and mass vaccination results in Cuba.' *In NIPH Annals*, pp. 195–210.

Simmons, R. D., Kirwan, P., Beebeejaun, K., Riordan, A., Borrow, R., Ramsay, M. E., Delpech, V., Lattimore, S. and Ladhani, S. (2015) 'Risk of invasive meningococcal disease in children and adults with HIV in England: a population-based cohort study.' *BMC Medicine*, 13, December.

Sobanski, M. A., Barnes, R. A. and Coakley, W. T. (2001) 'Detection of meningococcal antigen by latex agglutination.' *Methods in Molecular Medicine*, 67 pp. 41–59.

Stansfield, R. E., Masterton, R. G., Dale, B. A. and Fallon, R. J. (1994) 'Primary meningococcal conjunctivitis and the need for prophylaxis in close contacts.' *The Journal of Infection*, 29(2) pp. 211–214.

Sunderland, W. A., Harris, H. H., Spence, D. A. and Lawson, H. W. (1972) 'Meningococcemia in a newborn infant whose mother had meningococcal vaginitis.' *The Journal of Pediatrics*, 81(4) p. 856.

Swartley, J. S., Liu, L. J., Miller, Y. K., Martin, L. E., Edupuganti, S. and Stephens, D. S. (1998) 'Characterization of the gene cassette required for biosynthesis of the (α1→6)-linked N-acetyl-D-mannosamine-1-phosphate capsule of serogroup A Neisseria meningitidis.' *Journal of Bacteriology*. American Society for Microbiology (ASM), 180(6) pp. 1533–1539.

Taha, M. K., Deghmane, A. E., Antignac, A., Zarantonelli, M. L., Larribe, M. and Alonso, J. M. (2002) 'The duality of virulence and transmissibility in Neisseria meningitidis.' *Trends in Microbiology*, 10(8) pp. 376–382.

Taha, M.-K. (2002) 'Molecular detection and characterization of Neisseria meningitidis.' *Expert Review of Molecular Diagnostics*, 2(2) pp. 143–150.

Tan, L. K. K., Carlone, G. M. and Borrow, R. (2010) 'Advances in the development of vaccines against Neisseria meningitidis.' *New England Journal of Medicine*. Massachussetts Medical Society, 362(16) pp. 1511–1511.

Thabuis, A., Tararbit, K., Taha, M.-K., Dejour-Salamanca, D., Ronin, V., Parent du Chatelet, I. and Spaccaferri, G. (2018) 'Community outbreak of serogroup B invasive meningococcal disease in Beaujolais, France, February to June 2016: from alert to targeted vaccination.' *Eurosurveillance*, 23(28).

Tinsley, C. and Nassif, X. (2001) 'Meningococcal pathogenesis: at the boundary between the pre- and post-genomic eras.' *Current Opinion in Microbiology*, 4(1) pp. 47–52.

Tinsley, C. R. and Nassif, X. (1996) 'Analysis of the genetic differences between Neisseria meningitidis and Neisseria gonorrhoeae: two closely related bacteria expressing two different pathogenicities.' *Proceedings of the National Academy of Sciences of the United States of America*, 93(20) pp. 11109–11114.

Trotter, C. L. and Maiden, M. C. J. (2009) 'Meningococcal vaccines and herd immunity: lessons learned from serogroup C conjugate vaccination programmes.' *Expert review of vaccines*, 8(7) pp. 851–861.

Urwin, R. and Maiden, M. C. J. (2003) 'Multi-locus sequence typing: a tool for global epidemiology.' *Trends in Microbiology*, 11(10) pp. 479–487.

Van Amersfoort, E. S., Van Berkel, T. J. C. and Kuiper, J. (2003) 'Receptors, mediators, and mechanisms involved in bacterial sepsis and septic shock.' *Clinical Microbiology Reviews*. American Society for Microbiology (ASM), 16(3) pp. 379–414.

Van Deuren, M., Brandtzaeg, P. and Van Der Meer, J. W. M. (2000) 'Update on meningococcal disease with emphasis on pathogenesis and clinical management.' *Clinical Microbiology Reviews*. American Society for Microbiology, 13(1) pp. 144–166.

Varki, A., Schnaar, R. L. and Schauer, R. (2017) 'Sialic Acids and Other Nonulosonic Acids.' *In* Varki, A., Cummings, R., and Esko, J. (eds) *Essentials of Glycobiology [Internet]*. 3rd ed., Cold Springs Harbor (NY): Cold Spring Harbor Laboratory Press.

Vaughan, K., Ozaltin, A., Mallow, M., Moi, F., Wilkason, C., Stone, J. and Brenzel, L. (2019) 'The costs of delivering vaccines in low- and middle-income countries: Findings from a systematic review.' *Vaccine: X*, 2, July.

Vernikos, G. and Medini, D. (2014) 'Bexsero® chronicle.' *Pathogens and Global Health*, 108(7) pp. 305–316.

Vogel, U., Taha, M. K., Vazquez, J. A., Findlow, J., Claus, H., Stefanelli, P., Caugant, D. A., Kriz, P., Abad, R., Bambini, S., Carannante, A., Deghmane, A. E., Fazio, C., Frosch, M., Frosi, G., Gilchrist, S., Giuliani, M. M., Hong, E., Ledroit, M., Lovaglio, P. G., Lucidarme, J., Musilek, M., Muzzi, A., Oksnes, J., Rigat, F., Orlandi, L., Stella, M.,

Thompson, D., Pizza, M., Rappuoli, R., Serruto, D., Comanducci, M., Boccadifuoco, G., Donnelly, J. J., Medini, D. and Borrow, R. (2013) 'Predicted strain coverage of a meningococcal multicomponent vaccine (4CMenB) in Europe: A qualitative and quantitative assessment.' *The Lancet Infectious Diseases*, 13(5) pp. 416–425.

Whaley, M. J., Joseph, S. J., Retchless, A. C., Kretz, C. B., Blain, A., Hu, F., Chang, H.-Y., Mbaeyi, S. A., MacNeil, J. R., Read, T. D. and Wang, X. (2018) 'Whole genome sequencing for investigations of meningococcal outbreaks in the United States: a retrospective analysis.' *Scientific Reports*, 8, October.

WHO | Sentinel Surveillance (n.d.) WHO. World Health Organization. [Online] [Accessed on 18th March 2020] https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/sentinel/en/.

Yezli, S. (2018) 'The threat of meningococcal disease during the Hajj and Umrah mass gatherings: A comprehensive review.' *Travel Medicine and Infectious Disease*, 24, August, pp. 51–58.

Zumla, A. and Memish, Z. A. (2019) 'Risk of antibiotic resistant meningococcal infections in Hajj pilgrims.' *The BMJ*. BMJ Publishing Group, 366.