The role of national surveillance data in meningococcal conjugate vaccine programmes in England.

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Contents

Summary

The surveillance of vaccine preventable diseases is a fundamental part of national vaccination programmes. Data on the incidences of targeted diseases, their distribution within the population, measurement of disease severity, the uptake of vaccination and the way that the vaccine programme is viewed by those offered vaccination allows the success of a programme to be assessed and helps identify how the programme might be improved.

This thesis presents seven studies that show the importance of high quality national surveillance in designing and monitoring meningococcal conjugate vaccine programmes to offer optimal protection against MenC and MenW disease at a population level. Meningococcal disease is considered first together with the development of meningococcal vaccines and the sources of surveillance data available to monitor a national meningococcal vaccine programme.

The studies presented have provided estimates of the level and duration of the effectiveness of meningococcal conjugate vaccines against MenC disease, their impact on vaccinated and unvaccinated populations in England and have identified characteristics of those who are still at risk of this very rare disease. These studies also identified emergent meningococcal strains that have caused severe and unusual presentations of MenW disease, informed the immunisation strategies employed to best contain these increases and generated impact data and vaccine effectiveness estimates after vaccination against MenW disease was introduced. Further, a study of parental attitudes provided understanding of the way that parents

of young children view such vaccination programmes and their experiences with the health professionals and education materials that support them.

The combined findings of these studies show the importance of national surveillance data in supporting meningococcal conjugate vaccine programmes in England and ensuring that they provide optimal protection to populations at greatest risk of invasive meningococcal disease.

Chapter One

1. Introduction

High quality surveillance underpins decision-making before the introduction of a vaccine programme and it continues to inform post-introduction when changing epidemiology or further understanding of the impact of vaccine implementation may lead to programme adjustments. Invasive meningococcal disease (IMD) is a severe disease that can be life-threatening and it invariably requires hospital treatment. Long-term complications from the disease which can be life-changing arise in around 10% of cases and include limb amputation, deafness and brain damage. IMD incidence is highest in infants with secondary peaks in teenagers and older adults aged 65 years and over. New meningococcal vaccines that were effective in infants and were expected to offer long-term protection were licensed in 1999 and England was the first country to introduce these vaccines into its national infant programme that year with all other children up to 18 years also offered vaccine in a catch-up programme. These vaccines provided the first opportunity to have a marked, long-lasting impact on the profile of IMD in England and in other countries.

This thesis presents seven observational studies from work carried out between 1998 and 2018, covering 20 years of enhanced surveillance of IMD in England and the first routine use of meningococcal vaccines. This introductory chapter (Chapter One) begins with an overview of IMD and meningococcal vaccines, the role of national surveillance in monitoring disease and vaccination programmes, surveillance methodology and the development and licensure of meningococcal group C (MenC) vaccines. Chapter Two presents the first set of three studies on meningococcal group C conjugate (MCC)

vaccines in the UK and how these and other studies contributed to the further understanding of MCC vaccines. Evidence from clinical trials showed that MCC vaccines induced an immune response that was expected to provide long-lasting protection against IMD but evidence of actual protection against clinical disease was not available before the vaccines were licensed and introduced into the UK programme. Studies presented in this work provided evidence that the MCC vaccines reduced MenC disease in the population and estimated the duration of protection and level of effectiveness of these vaccines. This was determined in different age groups using data generated through enhanced national surveillance where every confirmed case of IMD is followed up for additional details on vaccination history and clinical features of the disease.

Chapter Three focusses on the epidemiology of a more recent meningococcal group W (MenW) outbreak in the UK and how decisions on the most effective use of MenACWY conjugate vaccines in targeted populations were informed by what had been learnt through IMD surveillance following MCC vaccine introduction. These studies helped to identify the emergence of a particularly severe strain of IMD which was important for changes that were made to vaccine offered to teenagers and for measuring how successful this strategy was. Three studies are presented that summarise the MenW outbreak in the UK, which describe an unusual gastrointestinal presentation in teenagers, explanation of the rationale for the resultant MenACWY conjugate vaccination programme for teenagers and the demonstration of its early impact.

Chapter four presents a study on parental experiences of vaccinating their young children in England and their attitudes towards vaccines and information resources that support the programmes. Understanding what motivates parents to vaccinate or prevents them from vaccinating can help ensure they are better supported and

therefore help to maintain high uptake of vaccines and sustained disease control. Vaccination programmes can only be successful with the active participation of the targeted population and so it is important to understand where parents get their information from, their motivation for choosing to vaccinate or refusing vaccination for their child and to determine whom they trust to inform them about vaccination. Information derived from such studies can help to improve the content of information materials, make better use of different media to deliver such information and can be used to further engage health professionals who are delivering the programme.

1.1 Invasive meningococcal disease

Neisseria meningitidis is a Gram negative oval shaped bacterium that occurs in pairs (diplococcus), is highly adapted to colonisation of the mucosal surface of the nasopharyngeal tract of humans and is commonly carried there as a commensal without causing harm. This asymptomatic carriage is an important reservoir for infection, transmission to susceptible individuals and for the induction of individual immunity. Meningococcal bacteria are transmitted from one person to another by nasopharyngeal droplets or respiratory secretions, such as through intimate kissing. Transmission usually requires frequent or prolonged close contact with an infected individual and humans are the only known host. The bacteria can be carried in the nasopharynx for several weeks or months but if a person develops IMD this is usually within 10 days of acquiring the bacteria (Caugant and Maiden, 2009).

Meningococci do have pathogenic potential and can pass through epithelial cells and enter the blood stream where they may survive and multiply (Taha et al., 2002, Caugant and Maiden, 2009). IMD encompasses a range of diseases depending on the focus of infection but meningococci can commonly cross the blood-brain barrier to infect the cerebrospinal fluid (CSF) and meninges to cause meningitis (infection of the

meninges membrane around the brain and spinal cord) or large numbers of bacteria in the bloodstream lead to blood-poisoning (septicaemia) or both meningitis and septicaemia can arise in the same person. Atypical clinical presentations of IMD resulting from the migration of bacteria to different anatomical sites are rare but well-described and include pneumonia, septic arthritis, endocarditis and epiglottitis/ supraglottitis (Parikh et al., 2018, Ladhani et al., 2015, Gaschignard et al., 2013).

For parents and health professionals meningococcal disease is one of the most feared infectious diseases (Campbell et al., 2017, Yarwood et al., 2005) due in part to the speed with which symptoms can progress from non-specific flu-like symptoms to coma following meningitis or with septicaemia to life-threatening circulatory failure, multi-organ failure and impaired coagulation which can lead to mass internal bleeding. These developments can arise over a few days or in just a matter of hours and prompt administration of antibiotics can improve the outcome. In England, meningococcal septicaemia alone has been associated with case fatality rates of 9% overall, with nearly 5% of meningococcal meningitis cases having a fatal outcome (Parikh et al., 2018). Survivors of meningococcal septicaemia can suffer rare but severe complications such as chronic pain, limb amputations, skin scarring and grafts and skeletal consequences of growth plate injury (Pace and Pollard, 2012, Monsell, 2012). Meningococcal meningitis is associated with severe long-term sequelae among survivors, including sensori-neural deafness, visual impairment, epilepsy, cognitive impairment, cerebral palsy and psychological disorders (Lucas et al., 2016, Pace and Pollard, 2012, Strifler et al., 2016).

1.2 Risk factors for Invasive meningococcal disease

The reason that some individuals develop invasive disease following colonisation, whilst the vast majority do not, is not completely understood and likely to relate to,

human, environmental and bacterial characteristics (Gowin and Januszkiewicz-Lewandowska, 2018).

1.2.1 Human factors and invasive meningococcal disease

In the UK, meningococcal vaccination is recommended in people with asplenia/splenic dysfunction due to their high risk of developing overwhelming bacterial infection and those with complement disorders or receiving complement inhibitor therapy who are at increased risk of IMD because the complement pathway is important for the elimination of these bacteria by lysis (breakdown of the cell membrane)(PHE, 2013). Some risk factors have been identified that can cause damage to the upper respiratory tract and may then facilitate entry of the bacteria from the nasopharynx to the bloodstream, for example smoking, passive smoking or prior upper respiratory tract infections (Hadjichristodoulou et al., 2016, Olea et al., 2017). Those with human immunodeficiency virus (HIV) infection have also been identified as being at higher risk of IMD (Simmons et al., 2015). In addition, a family history of IMD has been reported to be associated with increased risk which suggests that genetic factors may be important in some cases for both susceptibility and likelihood of developing severe disease (Olea et al., 2017).

The majority of cases, however, arise in individuals who were previously healthy and have no known clinical risk factors for IMD. The highest incidence of IMD is in infants (Ladhani et al., 2012, Parikh et al., 2018) due to their immature immune system, whilst carriage rates are highest in teenagers due to increased mixing with new people (Christensen et al., 2010) and death rates are usually highest in older adults often with other underlying disease (Ladhani et al., 2012, Parikh et al., 2018). For those in an eligible age group a lack of appropriate vaccination also increases risk of IMD (Findlow, 2018).

1.2.2 Environmental factors and invasive meningococcal disease

Environmental factors linked to an increased risk of IMD largely relate to an increased likelihood of the acquisition of meningococcal bacteria. Therefore, crowded conditions are associated with increased risk, including in the home (Olea et al., 2017, Hadjichristodoulou et al., 2016), new mixing of young people in university halls of residence (Mandal et al., 2017) or as military recruits (Riordan et al., 1998) and in mass gatherings, notably the Hajj which is an annual Islamic pilgrimage to Mecca involving millions of Muslims from around the world (Yezli, 2018). The incidence of IMD is also associated with seasonal peaks. These are seen in the winter months in countries like England with a temperate climate and may be linked to both behavioural changes in those months with a tendency to spend more time indoors, but also the increase in respiratory viral infections with prior infection, particularly with influenza, a recognised risk factor for invasive disease (Cartwright et al., 1991). In sub-Saharan Africa IMD peaks during the dry season and is thought to be linked to the dust and low-humidity conditions of the environment (Greenwood, 2006).

1.2.3 Bacterial factors and invasive meningococcal disease

Certain meningococcal strains are known to be associated with the pathogenesis of more severe symptoms. Meningococci are grouped by using the antigenic differences in their polysaccharide capsule with 12 groups recognised on the basis of the structure the capsule. The capsule is not always expressed in organisms carried in the nasopharynx but is present on entering the bloodstream. The capsule is important to protect meningococci against antibody / complement mediated killing and offers resistance to phagocytosis. Only six capsular groups are associated with the onset of the disease and meningococcal groups B, C, W and Y most commonly cause disease in the UK. Meningococcal groups A and X also cause disease, notably in Africa, where

major epidemics arise periodically, with attack rates as high at 100-800 per 100,000 population. The polysaccharide that constitutes the meningococcal capsule is a polymer of sialic acid or composed of sialic acid derivatives, with the exception of the group X and A capsules which contains repeating units of N-acetyl-mannosamine-1-phosphate (Rouphael and Stephens, 2012). The C and B capsules are very similar and constructed of homopolymers (repeating units) of sialic acid. The structure of the group B capsule is identical to a molecule in the developing human foetal brain which means that it does not elicit a robust immune response in humans as it is recognised as a self-antigen and is an example of molecular mimicry. The serotypes and serosubtypes of meningococcal bacteria are based on outer membrane proteins called porins which are designated PorA and PorB respectively. These are highly variable and as not all can be identified by available typing reagents, non-typeable strains may be isolated.

Traditionally molecular typing has been based on multilocus sequence typing (MLST) targeting seven genes and classifying into sequence types (ST) based on changes in these genes. Meningococci are highly variable but the same ST can be found in different capsular groups. Meningococci are also classed by clonal complexes (cc) which are also known as lineages and consist of groups of related STs. A cc refers to a closely related group of strains likely to have a common genetic ancestry. A clonal complex includes several lineages of highly related isolates (clones) (Taha et al., 2002). Some 'hypervirulent' ccs have been identified that account for most of the IMD cases seen worldwide. This ability of some meningococcal strains to cause more disease than others is not completely understood. However, virulence relates to the polysaccharide capsule that offers protection from the host immune system as it is poorly immunogenic and other surface structures of the bacteria, such as those involved in attachment to host cells or that can stimulate the release of inflammatory mediators thereby leading to

septic shock (Green LR, 2019). Many meningococci do not have capsular loci and so cannot generate a capsule and are not associated with invasive disease in healthy individuals as they are killed by complement (Jodar 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 MenB strain thereby evading vaccine-induced immunity.

More recently, whole genome sequencing (WGS) has been used to distinguish meningococci by up to nearly 2200 genes thereby offering much higher resolution and an ability to distinguish between very closely related meningococci and determine the evolution of different strains. However, this is only routinely undertaken for cases confirmed by culture, which is isolation of the live organism from a sterile site. Databases have been developed to hold global information on the genetic characteristics of meningococci derived by MLST and WGS so that the distribution of isolates can be mapped according to how many difference there are in their core genes (Rouphael and Stephens, 2012).

Distribution of meningococci by capsular group, serotype, serosubtype and cc varies globally and over time. Meningococci can generate genetic diversity and a variety of antigens (a substance foreign to the body that evokes an immune response either alone or after forming a complex with a larger molecule). This may occur through genetic transformation whereby the genes from the remains of meningococci or related bacteria (e.g. the gonococcus) are incorporated into another meningococcal bacterium. The resultant mutations and the ability to switch genes on or off thus enables the bacterium to rapidly express different antigens (Jodar et al., 2002). Increases in IMD have been linked to the introduction of a new meningococcal cc to a population and reduction in the incidence of IMD may occur as immunity is generated within that

population (Mustapha et al., 2016, Mustapha and Harrison, 2017). Meningococcal group A (MenA) disease, for example, predominated across the meningitis belt of sub-Saharan Africa before effective vaccination for individuals aged 1-29 years was introduced from 2010 (Mustapha and Harrison, 2017) Similarly, the incidences of MenC disease increased in some European countries in the mid-1990s and has since fallen following routine vaccination in some countries (Whittaker et al., 2017). Virulent strains include the clonal complex ST11 associated with MenC outbreaks in the 1990s and the MenW outbreak from 2014/15 (Stefanelli et al., 2009, Trotter et al., 2002, Ladhani et al., 2015b).

1.3 The public health importance of invasive meningococcal disease

IMD is rare but is considered to be of major public health importance due to the rapidity with which it can progress, its high associated morbidity and mortality and the possibility of secondary cases arising, although such clusters are uncommon with around 95% of cases being sporadic. Early treatment of the case can improve outcome and early antibiotic prophylaxis can reduce the likelihood of disease in close contacts by removing any carried organisms and reducing the likelihood of acquisition of *N. meningitidis* in the short term. The only way to prevent IMD on a population level, however, is through the use of an effective vaccine and many countries now have routine vaccination programmes that target the most common groups of meningococcal bacteria in their populations. This includes widespread use of MCC vaccines in Europe (Whittaker et al., 2017), adolescent MenACWY vaccination in the USA (ACIP, 2011, Black and Block, 2013) and the introduction of MenA vaccination across all countries in sub-Saharan Africa known as the ‘meningitis belt’ (WHO, 2014).

1.4 Group C meningococcal conjugate vaccines

1.4.1 Development and licensure of meningococcal group C conjugate vaccines

The earliest vaccines developed against meningococcal disease were prepared from heat-killed bacteria at the beginning of the 1900s, but these vaccines were reactogenic and of questionable efficacy (Vipond et al., 2012). Meningococcal polysaccharide vaccines were first developed in the 1940s. However, it was shown that immunogenicity required higher molecular weight polysaccharides, and thus effective capsular polysaccharide vaccines were developed in the 1960s and shown to be highly effective in clinical studies. These vaccines contain purified capsular polysaccharide and therefore targeted capsule-specific meningococcal disease. Meningococcal polysaccharide vaccines elicit a T-cell independent response and induce protective serum bactericidal antibodies (SBA) in older children and adults. However, such group C meningococcal polysaccharide vaccines are not effective in infants and toddlers who produce low avidity antibody (antibody that does not bind strongly to its target antigen) and thus the vaccine lacks SBA activity (Harris et al., 2003).

SBA protects against disease by activating complement-mediated lysis of the bacteria and / or opsonisation (Jodar et al., 2002). The lack of T-cell activation evokes a poor immunological memory response and only short-term levels of protective antibodies (Vipond et al., 2012) thereby requiring repeat vaccinations for long-term protection. Immunogenicity data, however, suggested that repeated doses of MenC polysaccharide vaccine led to immune hyporesponsiveness (a lowered immune response to subsequent doses) to the vaccine although the clinical significance of this was not clear (Jokhdar et al., 2004). These polysaccharide vaccines were therefore not suitable for routine population based programmes but were used in high risk groups, including pilgrims travelling to the Hajj in Saudi Arabia, and in outbreak situations.

In the 1990s meningococcal vaccines were further developed using chemical conjugation technology whereby the capsular polysaccharide was converted to a T-cell dependent antigen by joining it to highly immunogenic carrier proteins. In this case, the carrier proteins were tetanus toxoid and the non-toxic mutant of diphtheria toxoid, CRM_{197}. MenC meningococcal conjugate vaccines underwent an accelerated five year collaborative research programme in England supported by the Department of Health, the Public Health Laboratory Service, the National Institute for Biological Standards and Control, the Centre for Applied Microbiology and Research (all three public funded bodies now subsumed into Public Health England, PHE) and an academic immunobiology unit at the institute of Child Health in an organisation known at the National Vaccine Evaluation Consortium (NVEC). This MCC vaccine development work was given priority by NVEC due to the emergence of a highly virulent MenC ST-11 clonal complex in the UK in the mid-1990s. At that time there was promising early development of conjugated MenAC vaccines. In addition the successful introduction of conjugate vaccines against *Haemophilus influenzae* type b (Hib) disease with a resultant marked decrease in Hib disease clearly showed how effective such conjugated vaccines were (Slack et al., 1998).

1.4.2 Understanding of group C meningococcal conjugate vaccines at licensure

New MenC conjugate (MCC) vaccines were developed from capsular polysaccharide joined or conjugated to highly immunogenic carrier proteins (tetanus toxoid or CRM_{197} the non-toxic mutant of diphtheria toxIN). The licensure of these vaccines was based on immunogenicity and safety data. The Medicines and Healthcare products Regulatory Agency (the UK medicines licencing authority) accepted these data in recognition of the difficulty of generating clinical efficacy data to show a lower risk of a rare disease like IMD in an immunised cohort, compared to cohorts who were

unimmunised or immunised with a comparator vaccine (Miller et al., 2001). MenC disease affected around 2 people per 100,000 in the population in England each year at that time and vast clinical trials would have been required to show the vaccines protected against MenC disease. The research programme undertaken by NVEC therefore focussed on Phase II clinical trials to generate the safety and immunogenicity data required to inform licensure of the MCC vaccines and policy decisions for implementation of a MCC vaccination programme. Three vaccine manufacturers also collaborated on this programme of research providing: tetanus toxoid conjugated vaccine (Neis-vac^{TM}) by Baxter Biosciences; CRM_{197} conjugated vaccine by Wyeth (Meningitec^{TM}) and Novartis (Menjugate®). Licensure was based on the extrapolation of established serologic correlates of protection for plain serogroup C polysaccharide vaccines for infants (Farrington, 2001).

In this suite of cohort studies, the MCC vaccine was administered at 2, 3 and 4 months of age as part of a routine infant schedule (Richmond et al., 1999a, Richmond et al., 2001a), and as a single dose in toddlers (Richmond et al., 2001b), in school aged children (Burrage et al., 2002) and in adults (Richmond et al., 1999b). Comparator groups received different MCC vaccines or were earlier cohorts that had not received the MCC vaccine but were followed up using the same methodology (Richmond et al., 1999a). This was to generate clinical trial data on the reactogenicity, immunogenicity and priming for immune memory using MCC vaccine given at different ages. This was important given the limitations of the existing polysaccharide vaccines and how immunogenicity of these varied by age with protection of limited duration. Immunity to IMD was known to correlate with the presence of bactericidal antibody activity but the minimum level needed to provide immunity after vaccination was not known. These studies established that MCC vaccines induced high levels of bactericidal antibody to

group C capsular polysaccharide consistent with protection. Studies in infants also showed that SBA titres and serogroup-specific IgG levels following primary vaccination had fallen by 12 months of age. Subsequent boosting with either a polysaccharide or conjugate meningococcal vaccine induced significant antibody responses (both IgG concentration and SBA activity) providing evidence that the MCC vaccines primed the body for immunological memory (Richmond et al., 2001a).

At the time that MCC vaccines were first licensed, this memory was thought to be sufficient for long-term protection based on previous experiences with Hib conjugate vaccines (Booy et al., 1997). However, it was recognised that the high incidence of MenC disease in adolescence increased the importance of direct sustained protection against IMD whereas Hib was rare outside early childhood. As IMD had such rapid onset there were also theoretical concerns about the time needed to mount a protective antibody response (Richmond et al., 2001a). Thus, only the data obtained through post-licensure surveillance could address these outstanding questions.

1.5 Surveillance of vaccine preventable diseases on a population level in England

Disease surveillance has been defined by the World Health Organization as “routine ongoing collection, analysis and dissemination of health data’ (WHO, 2008). In the context of vaccination programmes, surveillance data are collected to inform vaccine introduction, monitor the early period after a vaccine has been introduced, continually review several years after vaccine introduction and, where feasible, advise disease elimination or eradication strategies. High quality surveillance is crucial to confirm national or regional containment or elimination of a specified disease. Surveillance protocols, including laboratory investigations, need to be kept under review so that they can collect high quality data to inform these different stages of a vaccination

programme. Furthermore, surveillance is essential to identify outbreaks or clusters of IMD and to aid decision-making in these scenarios.

1.5.1 Data sources for invasive meningococcal disease surveillance in England

1.5.1.1 Notification data

Every case of IMD requires public health management in order primarily to trace any contacts of the case and ensure they are appropriately offered antibiotic chemoprophylaxis and vaccination. This public health function is undertaken by PHE Health Protection Teams (HPT) in the local area of the case. In England, it has been a statutory requirement since the early 1900s that clinically diagnosed cases of meningitis and meningococcal septicaemia (from mid-1980s) are notified by registered medical practitioners in charge of the case to a local 'proper officer' at their local HPT who then reports this to a national body, now Public Health England (PHE, 2010). There is therefore a national record of notified cases of IMD that is designed to be a rapid reporting system as laboratory confirmation is not a pre-requisite for notification. These notifications retain information on gender, age in years and Regional location.

1.5.1.2 Hospital admissions data

IMD is invariably severe enough to require hospital admission and has a high associated case fatality rate. This means that hospital admissions data and death data are useful in IMD surveillance. Every hospital admission in England is coded for diagnosis on discharge based on standardised International Statistical Classification of Diseases and Related Health Problems or ICD coding (ICD-10 from 2010, ICD-9 prior to this) primarily in order to pay hospitals for the care they deliver. ICD codes are defined by the World Health Organization through a series of categories so that clinical conditions and diseases can be assigned codes in a systematic way (WHO, 2016). Hospital admissions data can also be used for research purposes and additionally

include information on age group, ethnicity and gender of the patient, dates of admission and discharge, hospital location, ICU admission, interventions undertaken during admission and discharge details, including if the patient was deceased.

Hospital episode statistics and notifications do not provide details of the infecting organism so, whilst an admission may be coded to IMD, it will not inform on the meningococcal capsular group and this is important when collating information regarding vaccines that target a particular capsular group.

1.5.1.3 Laboratory confirmed cases and enhanced surveillance

Laboratory-confirmed cases can be used as a surveillance source on a population level when a high proportion of clinically diagnosed cases are investigated. The testing carried out is highly sensitive and specific and the data can be collated nationally. This data has the advantage of including the capsular group of the causative meningococcus together with information on date of birth, date of specimen, location and gender. In England, the PHE Meningococcal Reference Unit (MRU) provides a national service for confirming and serogrouping all invasive meningococcal isolates as well as a free national PCR-testing service of clinical samples from patients with suspected IMD. All laboratory-confirmed cases of IMD are referred to the PHE immunisation team and group C IMD cases have been followed up as part of national enhanced surveillance since 1999 in order to determine vaccination history, travel history, place of birth and any underlying medical conditions. Laboratory-confirmed cases form the primary data source in most of the studies presented. Case ascertainment for IMD has been shown to remain very high under this surveillance strategy with only 73 laboratory confirmations identified outside the 5115 in the MRU dataset between 2007 and 2011(Ladhani, Waight et al. 2015). Enhanced surveillance was extended to the follow-up of all laboratory-confirmed cases of IMD from September

2015 with the introduction of a new MenB infant vaccination programme and a MenACWY vaccination programme for teenagers.

1.5.1.4 Death data

PHE has access to individual level Office for National Statistics (ONS) death data and where IMD, meningococcal meningitis, meningococcal septicaemia and other related conditions (based on ICD10 coding) have been identified as the underlying cause of death; these data are linked with laboratory records to determine the capsular group of the causal strain. In addition, the NHS patient demographic system (PDS) record can be used to ascertain whether patients died within a specified period of disease onset (to 28 days post disease onset, for example), through linkage with known cases.

1.5.1.5 Data from Public Health management of cases

From 2010, a centralised electronic record has been retained of the public health action undertaken by local HPTs. These details are documented on the HPZone software system. HPZone is web-based software for public health management of infectious diseases used by HPTs throughout England. Such electronic public health management records can be accessed, with permissions, in order to review individual cases for clinical details and vaccination history. This is also used as part of the resource for enhanced national surveillance with the revised PHE enhanced surveillance form available for completion within each recorded case of IMD. These forms can then be accessed centrally by the PHE immunisation team and the collected information retained on a case-specific record. Vaccination history collected through centralised enhanced surveillance and matched to every vaccine eligible laboratory-confirmed case is critical for the calculation of vaccine effectiveness.

1.5.1.6 Vaccine coverage data

Vaccine uptake data in the UK is collected under the Collection Of Vaccination Evaluated Rapidly (COVER) programme which has been running since 1987 (PHE, 2017a). PHE collates the UK immunisation coverage data from Child Health Information Systems (CHISs) for children at their 1st, 2nd and 5th birthdays in England in collaboration with the National Public Health Service for Wales, CDSC Northern Ireland and Health Protection Scotland. COVER data for local authority populations are extracted from CHISs and are submitted to PHE. All the data outputs are consistent with the current UK vaccination programme schedule and specified geographical boundaries through the COVER Information Standards Notice. Accurate measurement of vaccination coverage is key to evaluating the success of a vaccine programme and may be used in estimates of vaccine effectiveness. The strength of the UK COVER system is in the individual-based collection of vaccination status of a clearly specified population by a specific set of ages.

1.6 Surveillance preceding vaccine implementation

Consideration of whether a vaccine should be used in a certain population requires an in depth understanding of the epidemiology of that disease within the population, the disease incidence by age and sex, associated morbidity and mortality by age and sex and natural history of the disease including routes of infection. This enables a vaccine programme to target those most at risk of morbidity and mortality from the disease in the most cost efficient way. Sometimes, indirect protection is an important component of a population-based programme, for example vaccinating only females against human papilloma virus (HPV) will not only directly protect them against cervical cancer and genital warts but also reduces HPV infection and therefore genital warts in heterosexual men and it also has the potential to reduce other HPV-associated cancers

(e.g. penile, oropharyngeal) (Malagon et al., 2018, Pillsbury et al., 2017, Bollerup et al., 2016).

It may be that new surveillance strategies need to be implemented before a vaccination programme is introduced to more fully capture the required data. In 1998, before the introduction of the MCC vaccination programme, enhanced surveillance was undertaken in five English regions by reconciling clinically diagnosed and laboratory-confirmed cases (Davison et al., 2002a, Davison et al., 2002b). This identified substantial under-ascertainment from laboratory ascertained cases. This form of surveillance was undertaken nationally in 1999 to give a more complete picture of the burden of MenC disease in England and Wales (Davison et al., 2002a) with the MenC vaccination programme introduced from November that year. Serological surveillance also has a role in generating a profile of disease-specific population immunity prior to vaccine introduction, where there is an accepted correlate of protection, which can help in programme planning and in reviewing the programme impact.

1.7 National surveillance following MCC vaccine implementation

A surveillance strategy was established by PHE (at that time the Public Health Laboratory Service) in 1999 when the importance of laboratory confirmation of cases became more important in order to monitor the specific vaccine impact on group C disease. A comprehensive surveillance strategy was recognised as being of fundamental importance as the UK was the first country to introduce a MCC vaccination programme and licensure was based on immunogenicity data rather than direct evidence of efficacy against disease. From the point of vaccine introduction all cases of confirmed or probable invasive group C disease in those under 20 years of age were followed up for MCC vaccination history; this age group extended as those eligible for MCC vaccination (born on or after 1 September 1981) aged.

It was important to introduce a clear definition for a laboratory-confirmed MenC case in order to ensure consistent reporting and high specificity so it was highly unlikely that a case of laboratory confirmed IMD was not a true case of disease. In practice, an IMD case was defined as clinical meningococcal disease with culture or PCR serogroup C positive samples taken from a normally sterile site or rash aspirate. Laboratory identification was essential for the surveillance of the MCC vaccination programme as MCC vaccines would not protect against other meningococcal capsular groups so the confirmation of a case of IMD had to include identification of the capsular group. This allowed vaccine preventable and non-vaccine preventable cases to be distinguished, MenC cases arising despite appropriate vaccination to be identified and trends in IMD due to different capsular groups to be monitored.

Clear outcomes were set out in the national surveillance strategy to address some of the issues that were not fully understood before MCC vaccines were introduced and were important for more complete understanding of the vaccines and how to maximise their use in the protection of the population. These objectives included measuring the impact of MCC vaccination on the serogroup and age profile of IMD; vaccine coverage by age/ cohort; calculations of vaccine effectiveness by age/ cohort and monitoring any changes in the genotypic characteristics of invasive and carried strains of meningococci (Salisbury, 2001).

The enhanced national surveillance strategy was updated prior to the introduction of the MenACWY and MenB vaccines in 2015 in order to ensure that it was extended to all IMD (PHE, 2015). Updates to the national meningococcal vaccination schedule have been based on robust scientific data generated by clinical trials of revised vaccination schedules and new vaccines. Careful monitoring of the changing disease epidemiology, improved understanding of the vaccine effectiveness and its impact on nasopharyngeal

carriage(Maiden et al., 2008) and routine surveys of parental attitudes towards vaccination have also generated robust scientific data . Such data will be considered further in Chapters 2 to 4. Whilst vaccine safety is also a key component of the surveillance strategy this will not be covered within this thesis detail as it is beyond the scope of the papers presented in this work.

Chapter Two

1. Meningococcal group C immunisation in England

1.1. Critical account of published work on group C meningococcal conjugate vaccines

Three publications have been selected that used national surveillance data to address some of the outstanding questions around MCC vaccines at the time these were first introduced into a national immunisation programme in the UK in 1999 (Miller et al., 2001). These papers built on earlier clinical trials and studies using surveillance data in England whose findings will be summarised before each paper contributing to this thesis is critically reviewed. This research helped inform policy decisions around the national meningococcal immunisation programmes in England and in other countries, notably the strategy for the introduction of MenA vaccine across sub-Saharan Africa (LaForce et al., 2018, LaForce et al., 2007).

1.1.1. Post-licensure studies of meningococcal group C conjugate vaccines

It has been highlighted that licensure of the MCC vaccines was based on safety and immunogenicity studies using laboratory markers that correlated with protection against disease. However, larger Phase III clinical trials to look at the efficacy of the vaccine against clinical disease had not been undertaken (Miller et al., 2001). High quality post-licensure surveillance was therefore a prerequisite for licencing agreements and this surveillance was established in England and Wales (both countries were under the remit of the Public Health Laboratory service and then the Health Protection Agency

which became Public Health England in 2013 when the remit became England only) prior to vaccine introduction. This surveillance aimed to address a number of outstanding uncertainties:

- Licensure was based on a correlate of protection, did MCC vaccines protect against invasive disease;
- What was the duration of protection against invasive disease following vaccination?;
- Would MCC vaccines impact on the acquisition of carriage of MenC organisms in the nasopharynx? and;
- If so would this lead to herd protection or;
- Would the resultant selection pressures lead to the expansion of more virulent non-C strains of the meningococcus?

A large-scale, cross-sectional nasopharyngeal carriage study was undertaken in adolescents aged 15-17 years attending school or college in eight regions across the UK. Samples were collected both before and after this age group was targeted for vaccination in the MCC catch-up component of UK immunisation programme (Maiden et al., 2008). This study established that MCC vaccination had reduced carriage of MenC with an estimated efficacy against carriage of 75%. MCC vaccination had a disproportionately greater impact on MenC ST-11 organisms associated with the MenC outbreak in the UK. This impact was consistent with a herd protection effect following vaccination of all teenagers nationally, in whom meningococcal carriage rates were highest (Christensen et al., 2010). The reduction in carriage was high enough to interrupt the transmission of group C meningococci across the whole population.

There had been some concern prior to MCC vaccine introduction that reduction in the carriage of group C meningococci might lead to an increase in meningococci of other capsular groups if they populated the vacant niche in the nasopharynx but also because of the potential for capsule switching in meningococci (Maiden et al., 2008, Ala'Aldeen et al., 2000). The study by Maiden et al (2008) indicated that MCC vaccination was protecting against the carriage of MenC bacteria but that the resultant depletion in carried MenC organisms was not leading to replacement by meningococci from other capsular groups. Replacement of MenC with MenB or MenW had been of particular concern because of their known association with outbreaks (Maiden and Spratt, 1999).

The herd protection effect was further demonstrated using enhanced national surveillance data collected in the 2001/2002 epidemiological year (running from the 1 July one year to 30 June the following year in order to consistently capture the peak winter months). This study found a 67% reduced rate of disease in unvaccinated children eligible for MCC vaccination (Ramsay et al., 2003). Further, the first evidence of short-term (i.e. within a year of vaccination) vaccine effectiveness against IMD at 94% (95%CI 86 to 97%) across all age groups from infants to adolescents was demonstrated. Evidence of the effectiveness of vaccination over a longer period was first presented in another UK study based on enhanced surveillance data from England and Wales in the four years after the introduction of the MCC vaccination programme (Trotter et al., 2004). This reported a significant fall in the MCC VE from 93% (95% CI, 67 to 99%) within a year of routine infant vaccination to -81% (95%CI, -7430 to 71%) at least a year after. The calculated VE in children immunised aged 5 months to 18 years as part of the catch-up campaign remained high a year or more after vaccination (90%, 95%CI 83 to 94%) but still fell significantly (p=0.03) compared to VE within a year (95%,

95%CI 92 to 97%). These findings suggested that the serological markers of strong booster responses and high antibody avidity that had been used to establish the induction of immunity in clinical trials did not accurately predict longer-term protection. It also provided evidence that vaccination after infancy might have a longer duration of protection. This was consistent with VE data from Spain where there was a two, four and six month infant schedule and catch-up for children aged under six years (Cano et al., 2004, Larrauri et al., 2005). Further, in the Netherlands, vaccination was routinely offered at 14 months with a catch-up phase to 18 years and no vaccine failures had been reported within the first two years of the programme (de Greeff et al., 2006).

Surveillance in a number of countries that had introduced MCC vaccination (for example, the Netherlands, Ireland, Spain, Australia and Canada) also consistently showed a MenC-specific direct and indirect impact on IMD disease under differing national schedules (Larrauri et al., 2005, de Greeff et al., 2006, Booy et al., 2007).In Canada, this was observed in provinces that first introduced MCC vaccination (Bettinger et al., 2009). These findings from a number of different countries that had introduced MCC vaccines validated the impact and VE data that had been generated from surveillance data in England across different vaccination schedules. Further, information on the longer-term protection conferred by MCC vaccines was however, required.

To enable MCC vaccines to be licenced without large-scale efficacy trials a reliable laboratory indicator of clinical protection against disease, or surrogate of protection, was required that facilitated protection against group C IMD. Serum bactericidal antibody (SBA) had been established as a surrogate of protection against group C IMD in military recruits in pivotal studies in the 1960s in which Goldschneider et al (1969) demonstrated that the risk of MenC disease in an individual could be predicted by

whether or not they had naturally-occurring serum antibody that killed group C meningococci in the presence of human complement (Goldschneider et al., 1969a, Goldschneider et al., 1969b). Group C plain polysaccharide vaccines invoked SBA activity targeting meningococci and were shown to confer protection (Gold and Artenstein, 1971). A laboratory measurement can be associated with protection, and thus with a surrogate marker, but may not measure the actual antibody or cellular activity that mediates protection and so is viewed as a 'correlate'. The agreed correlate of protection for licensure of MCC vaccines was based on the induction of SBA using rabbit complement (rSBA) as an indicator of protective efficacy based on the proportion of vaccinees achieving an rSBA titre of 8 or more. This cut-off point had been validated against SBA generated using human complement (hSBA; the gold standard correlate of MenC protection based on a titre of ≥4) in unvaccinated adults (Borrow et al., 2001). Observed short-term VE (7 to 9 months after vaccination) in different age cohorts (Andrews et al., 2003) was demonstrated. However, this had not been validated against a protective level in the longer term.

1.1.2. Study 1

Meningococcal C conjugate vaccine: the experience in England and Wales (2009)

1.1.2.1. Study 1 Aim

This study aimed to generate data on the MCC vaccine impact on MenC disease and deaths in immunised and unimmunised populations, to identify vaccine failures and calculate updated estimates of vaccine effectiveness and determine any evidence of serotype replacement or capsule switching (Maiden and Spratt, 1999).

1.1.2.2. Study 1 Summary

National surveillance data collated at PHE and based on laboratory confirmed IMD cases was used to update the epidemiology of MenC disease by year and age group up to 9 years after the introduction of the MCC programme. Deaths certified with meningitis or meningococcal infection as an underlying cause from the Office for National Statistics (ONS) dataset were linked with laboratory confirmed cases of IMD and MenC-specific deaths were thereby identified. Every confirmed MenC case was followed up with their General Practice (GP) or PHE Health Protection Team (HPT) to ascertain the vaccination status of cases that arose in individuals who were eligible for MenC vaccination. National COVER data (PHE, 2017a) provided the uptake rates of MCC vaccine in each catch-up cohort and for routine infant vaccination through time. The General Practice Research Database (GPRD) (Walley and Mantgani, 1997) was used for the first time to generate estimates of partial vaccination in infants (i.e. those who received only one or two doses as infants) to identify the proportions of infants who were fully vaccinated or completely unvaccinated in the general population of the same age. These data were used with the data on vaccine status to calculate updated VE estimates using the screening method which essentially compared the proportion of cases that were vaccinated with the proportion in a matched cohort without disease that were vaccinated (Farrington, 1993). MRU data on meningococcal serosubtypes was also used to look for evidence of capsule switching.

1.1.2.3. Study 1 New knowledge gained

This study provided evidence of a longer duration of a population impact in both immunised and unimmunised cohorts (a herd effect) together with evidence of a marked reduction in deaths from MenC disease that persisted to at least nine years

after MCC implementation. This paper showed that a herd effect was sustained over this time with a 90% reduction in disease in those aged 25 years and older in 2007/08 compared to cases in 1998/99, the year before MCC vaccine was introduced. Herd protection was also shown in infants under three months for the first time.

The vaccine history was obtained for 99% (585/591 cases) of those in eligible cohorts. Seventy-three breakthrough cases of MenC disease in individuals fully-vaccinated for age were identified and estimates of partial vaccination from the GPRD were used to generate updated effectiveness calculations to the end of June 2006. Vaccine effectiveness (VE) within 12 months was estimated at 95% (95% CI, 84–99%) and at only 7% (95% CI, −3733% to 85%) 12 months or more after routine immunisation. A significant fall in VE in the 3 to 18 year age groups was also confirmed but estimated VE remained high at 92% (95% CI, 85 to 96%) up to six years after vaccination. This confirmed high VE for up to a year after vaccination in infancy but that the effectiveness fell significantly from a year or more after administration of the last infant vaccine. It also demonstrated that whilst VE also fell significantly from a year after a single dose of MCC vaccine at an older age, the vaccine stayed highly effective with VE at 92% and tight confidence intervals.

This paper also presented data on B:2a serotypes taken as a marker of capsule switching (from C:2a to a B:2a) to generate virulent non-C organisms and these data were consistent with no capsule switching having occurred. This therefore provided reassurance that a highly virulent B:2a strain was unlikely to emerge as a result of the MCC vaccination programme.

1.1.3. Study 2

Meningococcal C conjugate vaccine: updated post-licensure surveillance in England and Wales covering vaccine effectiveness, correlates of protection and modelling predictions of herd immunity (2010)

1.1.3.1. Study 2 Aim

This paper updated the MenC epidemiology and estimates of VE to 10 years after the introduction of MCC vaccine. Further, it studied the correlation between observed VE and predicted VE in the longer-term based on the percentage of vaccinees with rSBA levels above putative protective thresholds. The likely duration of protection against carriage in the population, given the fall in VE with time but the continuing herd protection was also estimated.

1.1.3.2. Study 2 Summary

National surveillance data based on laboratory confirmed IMD cases together with ONS population data were used to generate MenC incidence data by age group and epidemiological year up to 10 years after the introduction of the MCC programme. The ONS data on deaths certified with meningitis or meningococcal infection as an underlying cause were linked with laboratory confirmed cases of IMD to generate information on MenC-specific deaths. A 98.7% fall in incidence across all age groups was demonstrated and a 99.1% reduction in those directly targeted by MCC vaccination (<20 years of age) in 2008/09 was apparent compared to 1998/99 the year before MCC vaccine was introduced.

Every confirmed MenC case in England and Wales was followed up with their GP or local Health Protection Team was to ascertain the MCC vaccine history. The

vaccination status of 99.7% (594/596 cases) of those in eligible cohorts was obtained. The VE estimates were calculated using the screening method (Farrington, 1993) and the time since vaccination was broken down into four time intervals at <12 months, 12 to 23 months, 24 to 35 months and >=36 months post infant vaccination.

Serum bactericidal antibody (SBA) persistence data were generated using rabbit complement (rSBA) in an earlier clinical trial in infants who received MCC vaccine at two, three and four months of age and who had blood samples taken before and four weeks after a different vaccine administered between six months and four years of age. The effectiveness predicted on the basis of the proportions of vaccinated individuals with rSBA titers at or above 4, 8, and 128 at different time intervals were compared with the VE based on MenC cases arising at the four different time intervals since vaccination to look for results which were consistent with observed effectiveness.

An age-structured mathematical model of meningococcal transmission, disease and vaccination, which incorporated the role of herd protection in the duration of protection at a population level, was used to predict the future epidemiology of serogroup C meningococcal disease in England and Wales. Updated VE estimates were used to set the parameters of the model and the change to a MCC vaccination schedule of three months, four months and 12 months of age in 2006 was incorporated.

1.1.3.3. Study 2 New knowledge gained

This study updated the evidence of a population impact in both immunised and unimmunised cohorts (a herd effect) that persisted at least ten years after MCC implementation. This demonstrated that more precise estimates of VE could be calculated with the larger number of cases available over a ten year period and showed no significant decline in effectiveness up to 9 years after MCC vaccination at 3-18 years

of age. This suggested that in 2009, these children continued to be protected after the single dose of MCC vaccine that they received in 1999-2000.

For the first time it was possible to break down VE estimates into smaller time intervals after routine vaccination in infancy. This demonstrated a gradual decline in VE estimates from 95.9% (95% CI, 86.6 to 98.8%) within 12 months to 30.7% (95% CI, -2,846 to 89.6%) 36 months or more after the third dose of the MCC vaccine. This was important as it showed a continued fall in VE after the first year and therefore suggested that the level of protection against MenC disease did not stabilise but that more children would become susceptible as the time increased since their last dose of MCC vaccine.

It was shown that the estimated VE based on MenC cases that had arisen more than 12 months post vaccination was consistent with measured declining rSBA levels. This enabled the continued use of a ≥8 titre cut-off for the rSBA assay, as it clearly showed that higher titres after vaccination did not correlate well with protection in the longer term. It was not possible, however, to validate rSBA titres of ≥4 because the confidence intervals were imprecise. This was important because long-term efficacy would seem to depend on persisting levels of circulating bactericidal antibody against the group C capsule in the body at the time of exposure rather than the ability to boost the production of antibodies following exposure. This paper modelled predictions of the population levels of MenC disease whilst incorporating the assumptions of the different durations of the protection against carriage for the first time; this was fitted to the observed incidence of disease. Thus, this model suggested that MCC vaccination induced between 3 and 10 years protection against MenC carriage.

1.1.4. Study 3

Meningococcal C conjugate vaccine: disease epidemiology, seroprevalence, vaccine effectiveness and waning immunity in England from 1998/99-2015/16 (accepted 2018)

1.1.4.1. Study 3 Aim

In this paper MenC epidemiology and estimates of VE were updated to 17 years after the introduction of the MCC vaccination programme in England and Wales. The 2014 seroepidemiology data and molecular characterisation data for invasive meningococcal isolates were also presented. The key aim was to identify which age groups within the childhood population in England were most vulnerable to MenC disease and whether the introduction of a MenC dose at 13-15 years helped to address any decreases in immunity. Case characteristics in older individuals were reviewed to determine whether any higher risk groups could be identified. Molecular characterisation of MenC isolates were also used to highlight any circulating strains of meningococci that might be of additional concern.

1.1.4.2. Study 3 summary

This study presented 17 years of surveillance following the introduction of MCC vaccination in England in 1999, the longest follow-up of a national MCC vaccination programme to date anywhere in the world. The UK MCC immunisation programme evolved over time and MCC-containing vaccine was offered to young people aged 13-15 years from 2013 to extend direct protection in teenagers and maintain herd protection in the wider population. In 2015, the MenACWY conjugate vaccine replaced the MCC vaccine in the teenage programme to help combat a national MenW outbreak. National surveillance data were used to evaluate the long-term impact of a national

MCC vaccination programme in England on MenC disease epidemiology and estimates of MCC VE up to 8 years or more following primary immunisation in infancy. Follow up of each case was with the GP and using data recorded on HPZone. Information from both sources was used to compile clinical and social characteristics for each individual case of MenC IMD.

Meningococcal genomes were obtained from the PubMLST Neisseria database and Meningitis Research Foundation Meningococcus Genome Library (MGL) where all the meningococcal isolates have been referred from England since July 2010.
Meningococcal cc11 core genomes referred from across the world were compared using the PubMLST genome comparator tool. The results were then mapped using SplitsTree4 with cc11 isolates from England highlighted to identify whether there were any particular strains that were important in England.
A profile of population immunity in 2014 was obtained using samples retained as part of the national serosurvey depository. SBA assays were performed against the group C target strain using these anonymised samples with pooled serum from young rabbits used as the complement source. One hundred samples were selected from cohorts to fit with different MCC vaccine schedules, based on age when collected in 2014. The findings were compared to three earlier surveys that used sera collected by the same Seroepidemiology Unit and tested using the same methods in the same PHE laboratory during 1996-1999 (Trotter et al., 2003), 2000-2004 (Trotter et al., 2008) and 2009 (Ishola et al., 2012). This was carried out to determine whether there had been any early impact on the immune profile of age groups offered MCC vaccine from 2013.

1.1.4.3. Study 3 New knowledge gained

This study identified that higher risk individuals in the highly vaccinated English population were 25-44 year old adults who were less likely to have received MCC vaccination (notably non-UK born) and had intense social mixing (for example, living in halls, hostels or other shared accommodation). Individuals with certain clinical conditions are considered at high risk for IMD and vaccination is recommended with MenACWY and MenB vaccine. No MenC cases were identified in individuals in these recognised high-risk clinical groups suggesting that the guidance is being followed and vaccination has been effective. Molecular characterisation of 121 of 122 available isolates between 2010/11-2015/16 showed that most (89/121, 73.6%) continued to belong to the hypervirulent ST-11 clonal complex (cc11) and that these had increased in number and proportion since 2010/11. It was shown that cc11 isolates in England were distributed amongst lineage 11.1 (35%), which had increased since 2010/11, and 11.2 (64%) mainly in several genetically closely related clusters. The identification of high numbers of lineage 11.2 isolates in 2015/16 in England was important as 11.2 populations of meningococci elsewhere have been described that have acquired traits (presumably from genetic exchange with *Neisseria gonorrhoea* which is highly related to *N. meningitidis*) that appeared to facilitate urogenital colonisation. This was observed in outbreaks of MenC disease in men who have sex with men (MSM) and in cases of urethritis in heterosexual males in the USA (Taha et al., 2016, Kupferschmidt, 2013, Bazan et al., 2017, Tzeng et al., 2017).

Updated VE estimates again indicated a rapid decline in protection from one year after routine infant immunisation. This confirmed that there was a rapid waning in protection following MCC vaccination in infancy regardless of whether a MCC-containing vaccine was also administered at 12 months of age (VE of booster at 12 months of age was -

43% but with wide confidence intervals (95% CI -5759 to 77%). This fall in protection was clearly seen in the levels of seroprotection against group C meningococci which were lowest in those aged 6-13 years in 2014. At a population level in 2014 there was some evidence of an increase in the proportion of adolescents aged 14-15 years with protective SBA titres following the introduction of a MCC booster dose for teenagers in 2013. A higher geometric mean SBA titre in this age group was found when compared to the same age group in 2009, before an adolescent MCC booster was introduced. This demonstrated that the MCC vaccine offered to teenagers had increased protection in this targeted age group.

Updated VE estimates for those who were immunised when aged 5-18 years in 1999-2000 (and aged 21-34 years in 2015/16) remained high at 95.0% (95% CI, 76.0 to 99.5%) up to at least eight years after vaccination. This study showed that only 20% of children who had been immunised with MCC vaccine in infancy with a booster dose at a year of age had protective SBA titers by 6-8 years. Importantly, it demonstrated that offering MCC vaccine at 13-15 years of age increased the proportion of these teenagers with protective SBA titers from 17% to 28% in the early stages of the programme. This study provided evidence of long-term protection following vaccination at an older age, based on VE estimated in those immunised at 5-18 years. This demonstrated that these young teenagers vaccinated at 13-15 years of age should remain protected as they move into an age of known increased risk of meningococcal carriage and IMD. This risk is known to be particularly high in new university students (Mandal et al., 2017)

Chapter 3

2. Meningococcal group W immunisation in England

2.1. Background to the meningococcal group ACWY vaccination programme

In early 2000, follow up of cases of MenW disease in national meningococcal reference laboratories in France and England identified that an unusually high number of MenW cases had occurred in pilgrims returning from the Hajj in Saudi Arabia and in their close contacts (Taha et al., 2000). Hajj-associated cases were also reported from a number of other countries globally, including more than 200 in Saudi Arabia (Taha et al., 2000). Unusually, a MenW hypervirulent ST-11 clonal complex (cc) was associated with the outbreak, which more typically occurs as group C but occasionally occurs as group B or W meningococcus. Prior to this outbreak a number of countries, including the UK, recommended meningococcal AC polysaccharide vaccine rather than MenACWY conjugate vaccine for travel. MenACWY vaccine was available in the UK from January 2001, and from mid-February 2001 was recommended for travellers to the Hajj. This outbreak was effectively controlled when the quadrivalent MenACWY conjugate vaccine became a Hajj visa requirement in 2002.

Subsequent increases in endemic MenW:cc11 disease were reported in sub-Saharan and South Africa from 2003, then Brazil and several other South American countries, with high case fatality rates (CFR) of up to 25% (Abad et al., 2014). With the exception of MenW increases associated with the Hajj outbreak, MenW cases have occurred in England at low levels. They have typically accounted for less than 5% of all IMD cases

each year (Ladhani et al., 2012). However, an increase in MenW cases began in England from 2009 (Ladhani et al., 2015) and this was due to the rapid expansion of a single clone belonging to the sequence type 11 clonal complex (cc11). Whole genome sequencing of recent invasive MenW cc11 isolates showed the South African strain arising from 2003 to be closely related to the original 'Hajj outbreak' strain whereas the South American strain that first arose in Brazil was genetically distinct from both of these strains (Lucidarme et al., 2015). The recent UK MenW outbreak strain has been shown to be distinct from the Hajj-associated strain but closely related to the South American strain and therefore likely to have originated there (Lucidarme et al., 2015) .

2.1.1. Critical account of published work on emergent MenW disease in England

Three publications have been selected that used national surveillance data to identify and track the emergence of a highly virulent MenW strain in England from 2009/10 which has since been isolated in other countries in Europe and other parts of the world, including Australia. These papers provided detailed information on the epidemiology of MenW disease in England which underpinned the decision to declare an outbreak and introduce a vaccination programme. Detailed follow-up of MenW IMD cases meant that an unusual presentation of symptoms was identified and described in teenagers. The early impact of the MenACWY adolescent vaccination programme in England on MenW disease was also analysed.

2.1.2. Study 4

Targeted vaccination of teenagers following continued rapid endemic expansion of a meningococcal group W clone (sequence type 11 clonal complex) (2015)

2.1.2.1. Study 4 Aim

This paper was published as a rapid communication to raise awareness in the European community. The MenW outbreak epidemiology was described in detail to share data that informed the decision of the expert advisory Joint Committee on Vaccination and Immunisation (JCVI) to offer MenACWY vaccine to all young people aged 14-18 years from August 2015 and to explain the rationale for the approach that was taken.

2.1.2.2. Study 4 Summary

This paper identified that in 2008/09 laboratory-confirmed cases of MenW accounted for 19 of 1109 (1.7%) IMD cases in England but had increased to the extent that it accounted for 170 cases (25% of all IMD) in the first 11 months of 2014/15. It was demonstrated that the rapid increase was driven by MenW isolates expressing PorB serotype 2a which is known to be a surrogate marker for MenW:cc11. This increase was first seen in adults but spread to teenagers, infants and pre-school children. It is not clear why this pattern emerged but it was likely to be linked to transmission being first established in adults through a link to South America where a closely related strain was endemic. Limited data on the clinical follow-up of cases collated as part of enhanced routine surveillance was presented. These data showed that most MenW cases had arisen in healthy individuals with no history of recent travel abroad consistent with this being an endemic strain. A quarter of cases had an unusual presentation such as pneumonia, septic arthritis and epiglottitis/ supraglottitis rather

than the more common septicaemia and meningitis. The reason for this was not known. The case fatality rate for MenW cases was 12%.

These data were part of the information used to inform the decision by the JCVI to introduce a programme to offer MenACWY vaccine to young people aged 13 to 18 years from August 2015. This public health action was summarised together with the full rationale for the programme which was a national emergency outbreak response. The MenACWY vaccine programme was expected to offer direct protection to adolescents but also herd protection in the wider population by targeting the age group with highest meningococcal carriage rates (Christensen et al., 2010).

2.1.2.3. Study 4 New knowledge gained

This work described the MenW epidemiology that led to the introduction of the MenACWY vaccine programme and emphasised the changes in case characteristics which had extended to include young children. High case fatality and atypical disease presentation associated with MenW were described, the latter of which was important for the recognition of MenW cases if they arose elsewhere. The outbreak details and the rationale for the action taken were presented to raise awareness in other European countries so that Public Health officials were primed to identify any cases that arose in their locality. This was timely since this emergent strain was later shown to be new to the UK (Lucidarme et al., 2015) and therefore could spread quickly in a naïve population with little immunity. An outbreak linked to a mass global scout event in Japan was subsequently identified with cases in Scotland and Sweden (Lucidarme et al., 2016) and other countries such as the Netherlands and Australia did subsequently report increases in MenW disease shown to be linked to the UK strain (Knol et al., 2017, Martin et al., 2016).

2.1.3. Study 5

Presentation with gastrointestinal symptoms and high case fatality associated with group W meningococcal disease (MenW) in teenagers, England, July 2015 to January 2016 (2016)

2.1.3.1. Study 5 Aim

This study described the clinical presentation of MenW cases in teenagers in England following anecdotal reports of cases in this age group presenting with unusual, predominantly gastrointestinal symptoms.

2.1.3.2. Study 5 Summary

A case review of 15 MenW cases in 15 to 19 year-olds in England that were laboratory confirmed by the MRU between July 2015 and January 2016 was undertaken. Clinical data were extracted retrospectively from HPZone and summarised for each case. This surveillance encompassed a time period subsequent to the targeted catch-up of the first group of school leavers to be covered by the MenACWY vaccination programme. No teenager in this case series, however, had received MenACWY vaccine before they developed MenW disease. All of the 15 teenagers were reported to be healthy prior to disease onset.

Seven of the 15 teenagers presented with predominant gastrointestinal symptoms (nausea, vomiting and/or abdominal pain) with diarrhoea in the 24 hours before attending hospital. Four cases of these seven had been diagnosed with gastroenteritis early in their illness and the typical non-blanching rash was only present in two of the teenagers after they arrived at hospital. Of the remaining eight cases, three had clinical presentations consistent with septicaemia (two cases) and meningitis (one case)

whereas four had recognised atypical presentations and the final case had non-specific, non-severe protracted symptoms. Six of 15 cases (40%) were fatal including five of the seven teenagers with gastrointestinal symptoms. Importantly IMD was often not initially considered as part of the differential diagnosis and public health actions were delayed – specifically chemoprophylaxis and vaccination of close contacts to minimise their immediate and longer-term risks.

2.1.3.3. Study 5 New knowledge gained

This was the first time that a predominant gastrointestinal presentation had been described in cases of IMD due to the MenW in Europe. This was an extremely atypical presentation although an extensive literature review identified a paper from Chile in 2013, where a MenW outbreak had arisen prior to the UK. This Chilean paper cited MenW mortality of 32% and diarrhoea was associated with a poor prognosis being significantly more common in fatal than non-fatal cases (56% vs 27%, p=0.034) (Moreno, 2013). The purpose of this paper was to ensure a high level of awareness amongst clinicians and public health colleagues of this unusual presentation to minimise the likelihood of similar cases being misdiagnosed, potentially delaying appropriate public health action. It led to collaborations with charities to update leaflets and other public-facing information. Further collaboration with the charities, Universities UK, UCAS and the three other UK countries led to the update of National (UK) Guidance on the prevention and management of meningococcal meningitis and septicaemia in higher education institutions (PHE, 2017b).

2.1.4. Study 6

Emergency meningococcal ACWY vaccination program for teenagers to control group W meningococcal disease, England, 2015–2016 (2017)

2.1.4.1. Study 6 Aim

This study presented data on the early impact of the MenACWY vaccination in teenagers in England after one year of the programme using newly enhanced national surveillance data.

2.1.4.2. Study 6 Summary

Rapid publication of the impact of the MenACWY vaccination programme was possible due to the near real-time reporting and follow-up of all confirmed cases of IMD in England. The national enhanced surveillance plan for meningococcal disease was revised to support the implementation of enhanced national surveillance for meningococcal disease prior to the introduction of both the MenACWY teenage and MenB infant vaccination programmes in 2015 (PHE, 2015). This was a retrospective observational study based on MRU confirmed cases of IMD that looked at one year's impact of the MenACWY vaccination programme on the first cohort of teenagers that were targeted. It was identified that there was a higher MenACWY vaccine uptake among new university entrants based on data automatically extracted from primary care databases in university-affiliated (n = 79) medical practices and non–university-affiliated (n = 7,543) practices for the 2015 school leaver cohort (56.1% vs. 33.8%; $p<0.0001$).

The overall increase in MenW IMD cases since the introduction of the programme was described in this work together with changes observed in specific age groups. Vaccine

impact on disease was estimated by comparing MenW, MenB and MenY cases in 2015-school leavers with disease trends based on total cases preceding the introduction of the programme. Projected numbers in the 2015/16 academic year were extrapolated from observed cases in those aged 19-24 years who were not targeted for MenACWY vaccination. The vaccine effectiveness in the targeted cohort was also calculated using the screening method (Farrington, 1993).

2.1.4.3. Study 6 New knowledge gained

This work demonstrated that there was a 69% decrease (95%CI 18% to 88%) in MenW disease in the cohort that left school in 2015 based on an observed 6 cases when 19.4 cases were predicted to occur. None of these cases had been vaccinated and therefore VE was estimated at 100% (95%CI -47% to 100%) whilst six of 17 (35%) MenB cases had received MenACWY vaccine, in line with national coverage data (36.6%). This provided good evidence of direct protection in the young people that were being vaccinated and was reassuring in the face of continued high case fatality in teenagers of 33% (6/18 cases). This work therefore showed that even modest uptake amongst school leavers could achieve significant impact. Importantly, this work demonstrated that university entrants were more likely to be vaccinated than their peers who were not at university (56.1% uptake vs. 33.8%; $p<0.0001$). First year university students had previously been shown to be at >12 times higher risk of ACWY IMD than their peers thus highlighting the importance of vaccination in these students (Mandal et al., 2017).

The incidence of menW disease across all age groups doubled between 2013/14 and 2014/15 from 0.17 to 0.35 cases per 100,000 population, but this then increased to only 0.40 per 100,000 in 2015/16. This was consistent with a slowing of the rate of increase in menW disease that had been observed prior to the introduction of the programme.

This was important as the programme strategy to target teenagers was based on the expectation that this would directly protect teenagers but also reduce disease in the wider population through an impact on carriage. These data suggested that an early herd effect may have been observed. The early impact of the MenACWY programme was thus reported rapidly to help inform other European countries in their decision-making around vaccination against MenW disease.

Chapter 4

3. Attitudes towards vaccination in England

3.1. Background to attitudinal surveys commissioned by PHE

The European Region of the World Health Organization (WHO) recommends that national uptake of at least 95% should be achieved for vaccines that prevent diseases targeted for regional elimination or control (WHO, 1999). This 95% coverage is also the target for other vaccines included in the UK vaccination programme before the fifth birthday of all children (Screening & Immunisations Team, 2017). The NHS Constitution for England (DHSC, 2015) sets out that the right to vaccination:

'You have the right to receive the vaccinations that the Joint Committee on vaccination and Immunisation recommends that you should receive under an NHS-provided national immunisation programme.'

It further acknowledges this as a reciprocal accountability and sets out a responsibility for patients and the public to:

'Please participate in important public health programmes such as vaccination.'

Since the early 1990s, high vaccination coverage has been achieved for the routine infant, childhood and adolescent programmes. Provisional English data showed that children who reached 18 months of age between January and March 2018 achieved 95.3% coverage for one dose of MenB vaccine, 92.9% for two doses and 86.7% for the booster dose (England, 2018) with uptake of the MenC-Hib vaccine given at 12

months of age reaching 91.5% by 2nd birthday and 92.6% by 5th birthday (Screening & Immunisations Team, 2017). This demonstrated a high level of confidence and acceptance of the routine childhood infant vaccination programme in England and/or compliance with NHS recommendations.

National surveys have been undertaken in England since 1991 to collect information on parental knowledge, beliefs and attitudes towards the immunisation programmes and their experiences with immunisation services when taking their infants and children to be vaccinated (Yarwood et al., 2005). These surveys are commissioned by Public Health England (PHE) with the questionnaires developed by PHE but the interviews conducted by a market research organisation using a door to door approach in randomly selected and representative locations. The interviewers seek households with children under five years of age where a parent or guardian is willing to participate in a survey about healthcare of young children. The primary purpose of these surveys is to inform planning of the immunisation programmes.

Even when vaccine uptake is high, the needs of parents can change. This may be seen if programmes are revised; as with the introduction of a second dose of MMR vaccine. When new vaccines are introduced there may be a need to inform about the diseases that the vaccine protects against and the vaccine itself. There may be specific issues around a vaccine, such as the risk of fever after MenB vaccine, which meant that paracetamol was recommended before vaccination. There may also be intense media interest and reporting and, more recently, social media activity which may raise concerns about vaccine safety such as the discredited link between MMR vaccine and autism (Ramsay et al., 2002) or which may increase the demand for a vaccine. It is important for this parental feedback to be current to identify any shifts in parental opinions on vaccines and diseases targeted by vaccination programmes.

3.1.1. Study 7

Changing attitudes to childhood immunisation in English parents (2017)

3.1.1.1. Study 7 Aim

This paper presents data on parental views of immunisation issues and experiences based on a 2015 survey of parents of young children, to compare these with the findings of similar surveys undertaken in an earlier 10 year period and to highlight any changes that were apparent since the most recent previous survey in 2010.

3.1.1.2. Study 7 Summary

This PHE survey of parental attitudinal surveys (Yarwood et al., 2005) was re-established and extensively revised in 2015 to make it relevant to the current immunisation programme, such as the introduction of immunisation in pregnancy against influenza and pertussis (Campbell H, 2015). This survey was conducted by a market research organisation commissioned by PHE to undertake this nationally representative survey of primary care givers (referred to as parents) of children aged under five years on its behalf. Parents were recruited using a door-to-door approach in locations that were randomly selected and stratified by region and index of multiple deprivation quintile (where every small geographical area in England is ranked from most deprived area (1) to least deprived area (32,844) and these are then collated into 10 equal groups from least to most deprived). Parents were interviewed face-to-face in their home without prior knowledge that the study concerned immunisation. There were a maximum of 86 open and closed-ended questions. Interviews were completed with 1792 parents of whom 1130 had children aged 0-2 years and 999 had children aged 3-4 years. There were 337 parents with children in both age groups.

3.1.1.3. Study 7 New knowledge gained

This was the largest survey of parental attitudes undertaken in England. There is no other national survey of immunisation attitudes globally that has been undertaken with such consistent methodology over a prolonged period allowing comparisons over time as well as a current perspective of parental opinions and experiences. Parents who participated in the survey were unlikely to recall seeing, hearing or reading information that made them have doubts about getting their child(ren) vaccinated. In 2002, there were 33% of parents who recalled such information compared to 12% in 2015. Meningitis and septicaemia continued to be the diseases perceived as being the most serious with 82% and 78% of parents respectively rating these as 'very serious'. Most parents (90%) said that they automatically had their children vaccinated when they were due and this had significantly increased from 72% of parents reporting this in 2010. In line with this only 2% of parents refused a vaccine offered to their child(ren), compared to 9% in 2010. Parents had high levels of trust in health professionals and the NHS (90% agreed or strongly agreed that they trusted each of these).

It was found that 72% of parents discussed immunisation with health professionals and nearly half of these parents (47%) felt more confident about immunising their child after that discussion, including some who had already decided to vaccinate their child. It was found that parents who used chat rooms or discussion forums to seek information on immunisation were significantly more likely to have been exposed to information that gave them doubts about having their child(ren) immunised or persuaded them not to immunise (31% vs 8% amongst all parents).

This was also found for parents using NetDoctor (30%), Patient.co.uk (27%) and Facebook or Twitter (23%).

Vaccine hesitancy is defined by the WHO Strategic Advisory Group of Experts as "delay in acceptance or refusal of vaccination despite availability of vaccine services" and there has been a focus globally on this term (MacDonald, 2015). The findings from this study, however, suggested that this was not a global phenomenon and that 'vaccine hesitancy' was not an issue in England in 2015. Parents were highly likely (90%) to indicate that they automatically had their children vaccinated as recommended. The evidence that immunisation is seen by the majority of parents as normal practice could be shared with health professionals as only 0.5% of the participants delayed vaccination due to their concerns and 2% refused one or more vaccines for their child. This was important in highlighting that most parents immunise their children as a matter of routine.

There was evidence of a link between the use of the internet to seek information on immunisation and an increased likelihood of exposure to negative information around immunisation and a decision to delay or refuse vaccination. Whilst almost all parents had access to the internet (97%) they had higher levels of trust in health professionals who delivered the immunisation programmes. Further, advice from and communication with these professionals was shown to be key in influencing parental decisions and making them feel confident about vaccinating their children. This information has been used in training sessions with practice nurses, midwives and those training these health professionals to highlight their key role in immunisation.

Chapter 5

4. Discussion

These studies cover 20 years of national surveillance from the period preceding and then following the introduction of the first meningococcal conjugate vaccines, targeting group C disease, in 1999. These MenC studies aimed to provide longer term data on the impact of the MCC vaccination programmes, assess any herd protection effect and importantly estimate vaccine effectiveness (VE) which could not be generated by pre-licensure studies. These studies showed sustained impact on MenC disease levels in England and high levels of VE for at least eight years after primary vaccination at five years of age or older. Rapid waning of VE after primary vaccination in infancy and after a booster at around 12 months of age was also confirmed. These findings were used to support decisions around MCC vaccination schedule changes, in particular the introduction of a toddler and then teenage booster dose. Further, the studies confirmed the appropriate cut-off for SBA titres when correlating laboratory results with predictions of longer term population protection based on VE and generated modelling predictions on the duration of protection against carriage which have subsequently been shown to be consistent with this lasting for around 10 years. The most recent MenC study also provided current data on population levels of protection against MenC using SBA titres ≥8 which suggested some early impact from the introduction of teenage vaccination.

The studies highlighted the emergence of a new highly virulent strain of MenW in England and described an unusual gastrointestinal presentation seen in teenagers that was associated with high case fatality (Campbell et al., 2016). The

epidemiological details were used to help decide which vaccination programme would generate the best population protection and halt the rapid increase of MenW (Campbell et al., 2015). The studies described the vaccination strategy that was adopted in England, explained the rationale and later the uptake and impact using trend analysis in order to raise awareness throughout Europe. Finally parental attitudes of infants and young children were presented to highlight the high level of support for vaccination in this population in England, the high levels of trust in the NHS and the health professionals delivering the programmes (Campbell et al., 2017). This was important as it has been used in training those health professionals to make them aware of these positive attitudes amongst English parents in contrast to those cited in the media, which has a tendency to portray vaccines as controversial, and academia where the concept of 'vaccine hesitancy' has broad acceptance.

It is well-recognised that an integral part of the development and implementation of a successful immunisation programme is high quality surveillance. This is used to collect information to inform decisions around the introduction of different vaccines, monitor the delivery of the programme (vaccine uptake) and its impact on the targeted disease (Begg and Miller, 1990). Surveillance of a vaccine preventable disease should ideally be as sensitive and specific as possible but there tends to be a tension between these two characteristics. Comprehensive data are important before a vaccine programme is introduced to gain good understanding of the disease incidence and its distribution in the population in terms of morbidity and mortality. Once a vaccine programme has had an impact and the disease becomes less common then the specificity of the diagnosis may be more important in order to monitor true cases of disease and not similar disease with other underlying causes.

Laboratory confirmation has been critical in the surveillance of meningococcal vaccination programmes which have targeted specific capsular groups of meningococci that cannot be differentiated without laboratory techniques. The aim of surveillance of vaccine preventable diseases is to identify that an immunisation programme is working in the way that was intended and to identify potential problems which can then be investigated further. Surveillance of the MCC immunisation programme in England provided information that could not be generated through pre-licensure studies as the cost would have been prohibitive given the low incidence of MenC disease in the population (Miller et al., 2001). Analysis of these data has confirmed the high effectiveness of MCC vaccines in the short-term in infants but also the rapid waning of protection after vaccination in infancy therefore highlighting the need for a booster dose (Findlow, 2018, Campbell et al., 2010, Campbell et al., 2009). Such boosting helps sustain direct protection in the vaccinated individual but may also indirectly protect the wider population through herd protection. Conjugate vaccines have been shown to impact on carriage of *N meningitidis* and therefore transmission (Maiden et al., 2008). The understanding of the short-term protection derived from MCC vaccination in infancy or as a toddler, based on VE calculations, was subsequently validated by MenC susceptible cohorts identified by seroprevalence surveys (Ishola et al., 2012, Trotter et al., 2003, Trotter et al., 2008) and more recently the early impact of introducing teenage vaccination could be discerned in the 2014 seroprevalence data (Findlow, 2018).

Safety and immunogenicity studies have been important alongside studies based on surveillance and have shown comparable immunogenicity of reduced primary schedules compared with the 3-dose schedule (Southern et al., 2009, Findlow et al., 2012). This has allowed the 3-dose primary schedule to be changed to a 2-dose and

then single infant dose without any expected reduction in protection which is both cost-saving and frees up space in a busy immunisation schedule. Surveillance data have confirmed that such changes have not compromised the vaccine effectiveness or population control of disease (Campbell et al., 2010, Campbell et al., 2009, Findlow, 2018). The ongoing monitoring of MenC disease on a national level has recently enabled the final dose in the primary schedule to be removed, after a booster dose was introduced at 13-15 years in 2013. The introduction of a booster dose at 12 months of age and then 13-15 years of age were necessary to sustain direct protection in adolescence through an age of increased risk and also to maintain herd protection in the wider population to avoid a resurgence of disease in those who were not protected by prior vaccination (i.e. infants and older adults).

Enhanced surveillance of meningococcal disease in near real-time allowed the threat of a newly emerged MenW strain in England to be identified at an early stage (Ladhani et al., 2012) and to closely monitor and describe this so that an outbreak was declared and emergency vaccination introduced in a timely way (Campbell and Ladhani, 2016, Campbell et al., 2016, Campbell et al., 2015). The understanding of the importance of herd protection and the greater longer-term vaccine effectiveness after MCC administered at school age (Campbell et al., 2010, Campbell et al., 2009) together with awareness of the age profile of carriage of the meningococcus (Christensen et al., 2010) and increased risk of disease on entering university (Mandal et al., 2017) helped inform the decision-making around offering MenACWY vaccination to teenagers in 2015. The introduction of a new MenB vaccine in infants at around the same time also influenced this decision based on what was understood about its potential to protect against circulating MenW strains (Ladhani et al., 2016).

Experience of the surveillance processes and information required following MCC introduction ensured that a revised national surveillance protocol and accompanying surveillance forms were prepared and publicly available before the introduction of the MenACWY and MenB vaccination programmes (PHE, 2015). This assured continued high quality national surveillance which supported early analysis of the effectiveness and impact of the immunisation approach taken to control the emergent MenW disease at an early stage (Campbell et al., 2015). This differed from the approach that had been taken in Chile, where young children were vaccinated, and which did not appear to have any effect outside the targeted age groups (Safadi et al., 2015). The Campbell et al., 2015 paper resulted in higher awareness in other European countries and Australia where MenW was beginning to emerge (Broad and Snape, 2017, Hong et al., 2018, Martin et al., 2016).

The involvement of those being targeted by immunisation programmes, parents of infants and toddlers and teenagers in the programmes targeting MenC and MenW disease, are also key. Without their participation and acceptance no vaccine programme could be successful. In England, high quality surveillance of vaccine programmes includes large regular surveys of the attitudes of parents of young children (Campbell et al., 2017, Yarwood et al., 2005). The information generated by these surveys has supported the development of resources and awareness campaigns. When MCC vaccine was introduced, for example, it was known that meningococcal disease was greatly feared by parents and vaccine was likely to be in high demand. Therefore in the face of limited vaccine supplies and a staged catch-up campaign, which could not target all children aged 0-18 years at one time, the key message of the television commercial that aired when the vaccine was introduced was to ‘wait your turn’ in order to help manage expectation.

5. Conclusions

This collection of studies has shown the importance of high quality national surveillance in the development and evaluation of meningococcal conjugate vaccine programmes in England. The surveillance strategies adopted in England have ensured the availability of national data that has been collated and used to generate estimates on the level and duration of vaccine effectiveness against MenC disease, the MCC impact on vaccinated and unvaccinated populations in England and identified characteristics of those who are still at risk of this now very rare disease. These studies have identified emergent meningococcal strains that have caused severe and unusual presentations of MenW disease, informed the immunisation strategies employed to best contain these increases and then generated impact data and vaccine effectiveness estimates once the programme was introduced. Further, representative attitudinal surveys have generated information that provided an insight into the way in which parents of young children view such vaccination programmes and their experiences with the health professionals and education materials that support them.

6. Future work

The introduction of the MenB and the MenACWY vaccination programmes in 2015 meant that PHE guidance on public health management of meningococcal disease had to be reviewed and updated. Early advice was therefore made available on the management of clusters of MenB disease (Ladhani et al., 2014) and subsequently updated Public Health guidance was published in March 2018 (PHE, 2018). Genomic analyses are now a routine component of surveillance and these data have

furthered understanding of the origins of the current MenW outbreak in England and its spread to other countries (Lucidarme et al., 2015, Lucidarme et al., 2016) and it is important that collaboration with other countries such as the Netherlands (Knol et al., 2017) and France where MenW cases are increasing continues so that the experiences in England help inform decisions about vaccination in these countries. There is a need for a follow-up study of the impact and effectiveness of the MenACWY adolescent vaccination programme now that the programme has been in place for three years and updated seroprevalence would generate a population profile of immunity to MenW and MenC in particular following the MenACWY teenage programme. More detailed analysis of the gastrointestinal presentation of MenW cases through age- and sex-matched comparisons of such symptoms and disease presentation in individuals with MenY and MenB disease would clarify whether this is a specific association with group W disease and/or teenagers. Analysis of this has been undertaken and suggests that there may be a significant difference between the types of IMD caused by these three capsular groups and the ages they are more likely to occur. It is also important to continue to broaden the awareness of meningococcal disease in different medical specialities. A letter submitted to Journal of Infection highlights the need to consider an infectious cause after sudden death in young people. This is the case even if there is a history of social activity or behaviour which may increase suspicion for drug misuse, such as clubbing, recent recreational drug taking or alcohol consumption.

The scope for further attitudinal work is expanding as platforms for vaccination such as adolescence and pregnancy are increasing. PHE has commissioned successful surveys of health professionals involved in delivering vaccination programmes to pregnant women (Vishram et al., 2018) and it would be useful to better understand

the motivators for health professionals involved in infant and adolescent programmes so that training can be targeted appropriately. PHE has recently commissioned surveys of the views of adolescents and their parents on immunisation and initial results have highlighted the importance of school-based information on immunisation and of parental discussions. These findings will be fully analysed, published and fed back to the school nurses leading on adolescent vaccination programmes.

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Appendix One: List of published papers comprising the thesis

Published research relating to MCC vaccination with links to the work

Study 1. *Campbell, H., R. Borrow, D. Salisbury, E. Miller. Meningococcal C conjugate vaccine: the experience in England and Wales. Vaccine 2009. 27S: B20-B29.* https://www.sciencedirect.com/science/article/pii/S0264410X09006215?via%3Dihub

Study 2. *Campbell H, Andrews N, Borrow R, Trotter C, Miller E. Updated postlicensure surveillance of the meningococcal C conjugate vaccine in England and Wales: effectiveness, validation of serological correlates of protection, and modelling predictions of the duration of herd immunity. Clinical & Vaccine Immunology: CVI, May 2010, vol./is. 17/5(840-7), 1556-679X;1556-679X (2010 May).* https://cvi.asm.org/content/17/5/840.long

Study 3. *Findlow H, Campbell H (corresponding author), Andrews N, Lucidarme J, Borrow R, Ladhani S. Serogroup C Neisseria meningitidis disease epidemiology, seroprevalence, vaccine effectiveness and waning immunity, England, 1998/99 to 2015/16. Euro Surveill. 2019;24(1):pii=1700818. https://doi.org/10.2807/1560-7917.ES.2019.24.1.1700818* https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2019.24.1.1700818

Published research relating to the use of MenACWY vaccine to control an outbreak

Study 4. *H Campbell , V Saliba, R Borrow, M Ramsay, S N Ladhani 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, Volume 20, Issue 28, 16 July 2015 Rapid communications* *http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=21188*

Study 5. *H Campbell, SR Parikh, R Borrow, E Kaczmarski, ME Ramsay, SN Ladhani. Presentation with gastrointestinal symptoms and high case fatality associated with group W*

meningococcal disease (MenW) in teenagers, England, July 2015 to January 2016. Rapid communication Eurosurveillance, Volume 21, Issue 12, 24 March 2016 *http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=21422*

Study 6. *Campbell H, Edelstein M, Andrews N, Borrow R, Ramsay M, Ladhani S. Emergency Meningococcal ACWY Vaccination Program for Teenagers to Control Group W Meningococcal Disease, England, 2015-2016. Emerg Infect Dis. 2017 Jul 15;23(7). doi: 10.3201/eid2307.170236. https://wwwnc.cdc.gov/eid/article/23/7/17-0236_article.*

Published research relating to parental attitudes towards vaccination

Study 7. *Campbell H, Edwards A, Letley L, Bedford H, Ramsay M, Yarwood J. Changing attitudes to childhood immunisation in English parents. Vaccine. 2017 Apr 17. pii: S0264-410X(17)30441-3. doi: 10.1016/j.vaccine.2017.03.089.* https://www.sciencedirect.com/science/article/pii/S0264410X17304413?via%3Dihub

Appendix Two: List of all published papers based on surveillance data or around surveillance

1. Campbell H, Gupta S, Dolan GP, Smita J. Kapadia SJ, Singh AK, Andrews N, Amirthalingam G. Review of vaccination in pregnancy to prevent pertussis in early infancy. Journal of Medical Microbiology 2018. DOI 10.1099/jmm.0.000829
2. Bukasa A, Campbell H, Brown K, Bedford H, Ramsay M, Amirthalingam G, Tookey P. Rubella infection in pregnancy and congenital rubella in United Kingdom, 2003 to 2016. Euro Surveill. 2018 May;23(19). doi: 10.2807/1560-7917.ES.2018.23.19.17-00381. PubMed PMID: 29766840.
3. Parikh SR, Campbell H, Gray SJ, Beebeejaun K, Ribeiro S, Borrow R, Ramsay ME, Ladhani SN. Epidemiology, clinical presentation, risk factors, intensive care admission and outcomes of invasive meningococcal disease in England, 2010-2015.Vaccine. 2018 Apr 23. pii: S0264-410X(18)30212-3. doi:10.1016/j.vaccine.2018.02.038. [Epub ahead of print] PubMed PMID: 29699791.
4. Mandal S, Campbell H, Ribeiro S, Gray S, Carr T, White J, Ladhani SN, Ramsay ME. Risk of invasive meningococcal disease in university students in England and optimal strategies for protection using MenACWY vaccine. Vaccine. 2017 Oct 13;35(43):5814-5818. doi: 10.1016/j.vaccine.2017.09.024. Epub 2017 Sep 18. PubMed
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5. Bhavita Vishram, Louise Letley, Albert Jan Van Hoek, Louise Silverton, Helen Donovan, Cheryll Adams, David Green, Angela Edwards, Joanne Yarwood, Helen Bedford, Gayatri Amirthalingam & Helen Campbell. Vaccination in pregnancy: Attitudes of nurses, midwives and health visitors in England. Journal Human Vaccines & Immunotherapeutics. Volume 14, 2018 - Issue 1. http://www.tandfonline.com/eprint/mDerf2zJ7cebg5NyByyv/full
6. M.J. Knol,S.J.M. Hahné,J. Lucidarme,H. Campbell,H.E. de Melker,S.J. Gray,R. Borrow,S.N. Ladhani,M.E. Ramsay,A. van der Ende. Temporal associations between national outbreaks of meningococcal serogroup W and C disease in the Netherlands and England: An observational cohort study. The Lancet Public Health (2017)
7. Byrne L, Campbell H, Andrews N, Ribeiro S, Amirthalingam G.. Arch Dis Child 2017; 0:1–6. doi:10.1136/archdischild-2016-311802 http://adc.bmj.com/content/archdischild/early/2017/08/10/archdischild-2016-311802.full.pdf?ijkey=6qzDcJOfQ8h1zjS&keytype=ref
8. Lucidarme J, Lekshmi A, Parikh SR, Bray JE, Hill DM, Bratcher HB, Gray SJ, Carr AD, Jolley KA, Findlow J, Campbell H, Ladhani SN, Ramsay ME, Maiden MCJ, Borrow R.Frequent capsule switching in 'ultra-virulent' meningococci - Are we ready for a serogroup B ST-11 complex outbreak?J Infect. 2017 Aug;75(2):95-103. doi: 10.1016/j.jinf.2017.05.015. Epub 2017 Jun 1. http://www.sciencedirect.com/science/article/pii/S0163445317301639?via%3Dihub

9. Whittaker R, Dias JG, Ramliden M, Ködmön C, Economopoulou A, Beer N, Pastore Celentano L; ECDC network members for invasive meningococcal disease.The epidemiology of invasive meningococcal disease in EU/EEA countries, 2004-2014.Vaccine. 2017 Apr 11;35(16):2034-2041. doi: 10.1016/j.vaccine.2017.03.007. Epub 2017 Mar 14. http://www.sciencedirect.com/science/article/pii/S0264410X17303134?via%3Dihub
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12. Sustained Effectiveness of the Maternal Pertussis Immunization Program in England 3 Years Following Introduction.
Gayatri Amirthalingam; Helen Campbell; Sonia Ribeiro; Norman K. Fry; Mary Ramsay; Elizabeth Miller; Nick Andrews. Clinical Infectious Diseases 2016 63 (suppl 4): S236-S243 doi: 10.1093/cid/ciw559 https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciw559
13. 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. 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. Published online October 27, 2016 http://dx.doi.org/10.1016/S0140-6736(16)31921-3.

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