Meningococcal Carriage, Disease and Vaccination

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I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

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Date: 30/06/2019
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CONTRIBUTIONS

This thesis includes published papers and works for submission. Titles and detailed overview of each work are presented in the section: structure of this thesis, page 9-14.

Publication #1: I was the first and corresponding author; I contributed in searching the literature, extracting the data, synthesising evidence, and analysing the data, summarising and interpreting the results, and drafting the manuscript, and incorporated comments from co-authors. I responded to editors and reviewers during the submission process.

Publication #2 (in press): I was the corresponding and joint first author. In league with the first author, I searched literature, extracted data, drafted the first version of the manuscript and revised the subsequent versions. I responded to the editors’ and reviewers’ comments during the submission process.

Publication #3: I was the first author, contributed in searching the literature, extracting the data, summarising and interpreting the results. Subsequently, I drafted the manuscript, addressed comments from co-authors and, later on, from reviewers.

Publication #4: I was the first and corresponding author, participated in designing and conducting the survey, cleaned the raw data, performed the analysis and interpreted the findings. I drafted the manuscript, implemented suggestions and comments from the co-authors, and submitted the manuscript.

Publications #5: I was the first and corresponding author, participated in designing the questionnaire and conducting the survey, cleaned and collated the raw data, performed the analysis and interpreted the findings. Subsequently, I drafted the manuscript and implemented suggestions and comments from the co-authors. During the submission process I responded to editors’ and reviewers’ comments.

Publication #6: I was the first author, abstracted and synthesised the data, created the table, drafted the manuscript and implemented suggestions and comments from co-authors. During the submission process I responded to editors and reviewers.
Publication #7: I was the corresponding and joint first author, assembled the data, performed the statistical analysis with guidance from our institute’s statistician and interpreted the findings. I also drafted the manuscript and incorporated suggestions and comments from co-authors. During the submission process my role was to submit and respond to editors and reviewers.

Publication #8: I was the first and corresponding author, conducted literature review, carried out most of data cleaning and collation. Subsequently I carried out the statistical analyses with guidance from my supervisors, interpreted the findings and, created the tables and graphs, drafted the manuscript and incorporated comments from co-authors. During the submission process my role was to submit and subsequently address editors’ and reviewers’ comments. I also presented the results of the analysis orally at local seminars.

Unpublished RCT: My role included to design the questionnaire; to prepare applications for and obtain ethical approvals from Australia and Saudi Arabia. I also formed and trained a research team to recruit and follow up the participants. I also organised laboratory tests under the guidance of my supervisors. Subsequently, I analysed and interpreted the results, created the tables and graphs, drafted the manuscript and incorporated suggestions and comments from co-authors.

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Supervisor’s declaration:
As a supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

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Publication #4: Ethics approval has been obtained for the study from the Institutional Review Board of King Saud University College of Medicine, Saudi Arabia (Ref: E-17-2534).

Publication #5: The survey protocol and tools were reviewed and approved by the Institutional Review Board of King Abdullah Medical City in the Holy Capital, Saudi Arabia (Ref: 15-202).

Publication #7: Ethics approval for this trial was obtained from the Hunter New England Research Ethics Committee NSW, Australia (Ref: 13/05/3.05). The trial was conducted according to the International Conference on Harmonisation Good Clinical Practice guidelines. The trial is registered at the Australian New Zealand Clinical Trials Registry, registration number: ACTRN12613000536763.

Publication #8: Access to data was obtained by permission from the lead investigators of both trials. The ethics approval for the United Kingdom trial was approved by the Berkshire Research Ethics Committee, and the study protocol and informed consent forms for the Australian trial for each study centre were gained from local institutional review boards.

Permission to include all these publications in this thesis was either obtained from the publishers, or journal’s policy allowed me to include those in thesis without seeking further approval.

Unpublished RCT: the trial was reviewed and approved by the Health Research Ethics Committee of the University of Sydney, Australia (Ref: 2015/693, date: 04/01/2016), the Sydney Children's Hospitals Network Human Research Ethics Committee (Ref: HREC/16/SCHN/209), the Institutional Review Board of King Abdullah Medical City, Saudi Arabia (Ref: 16-266) and the Ministry of Health, Saudi Arabia (Ref: A00484). The trial was conducted according to the International Conference on Harmonisation Good Clinical Practice guidelines. The trial is registered at the Australian New Zealand Clinical Trials Registry, registration number: ACTRN12616001230448.
ABSTRACT

Invasive meningococcal disease (IMD) is caused by *Neisseria meningitidis*; a Gram-negative, aerobic encapsulated diplococcus that can cause large scale meningitis outbreaks. The risk of meningococcal carriage and disease is higher among particular age groups, certain community settings and travellers.

The prevalence of invasive meningococcal disease peaks during infancy due to lack of immunity and again, to a lesser extent, in late adolescence/early adulthood due to increased social mixing. Closed and semi-closed community settings are also associated with high rates of meningococcal transmission and carriage acquisition and have experienced recurrent outbreaks of IMD. Travelling, including pilgrimage to Hajj, is yet another vulnerable circumstance.

Despite advanced intensive care support, about 20% of survivors are left with long-term sequelae following IMD, thus prevention by vaccination is the most practical and effective measure of reducing the morbidity and mortality associated with IMD. The use of polysaccharide and then conjugate vaccines against specific meningococcal serogroups causing outbreaks led to a dramatic decline in IMD incidence. However, the observation of waning of immune responses over time following early childhood vaccination remains a concern for resurgence of disease in adolescence. Additionally, issues such as quantifying the effect of various meningococcal vaccines on carriage and the immune interaction between the carrier protein components of meningococcal conjugate vaccines and other vaccines containing the same proteins as antigens remain outstanding.

To this end, the purpose of this thesis is to explore ways to better protect vulnerable populations, focusing on vaccination coverage in settings where a mandatory vaccination
policy is in place, understanding the effect of vaccination on meningococcal carriage, and interpretation of the immune interactions between vaccines and changes to the immune response over time following vaccination.

This thesis considers the annual Hajj pilgrimage as an exceptional context to achieve its aims as it comprises two groups of at-risk individuals: travellers and those within a closed population, and pilgrims often receive multiple vaccines during their preparation to the Hajj journey including meningococcal vaccine.

Meningococcal vaccination is mandatory for domestic Hajj pilgrims and healthcare workers; however, their uptake has not been thoughtfully assessed. Hence, we evaluated the meningococcal vaccine coverage among these two groups and explored possible influencing factors. The uptake was suboptimal among both groups; gender, education, employment, receiving pre-Hajj health advice and distance of travel were important influencing factors and lack of awareness was the main barrier.

One possible way to compensate for the suboptimal vaccination coverage is to assess and, if possible, limit meningococcal carriage. Therefore, a randomised controlled trial was conducted primarily to explore if meningococcal conjugate vaccines are better than their polysaccharide counterparts in reducing nasopharyngeal carriage among Hajj pilgrims. Actually, among the 1146 participants, the carriage of meningococci was almost non-existent. This may be suggestive of a successful vaccination policy or, more likely, a low season of meningococcal carriage.

Hajj pilgrims, as travellers, are often required to receive multiple vaccinations within a short time period. These vaccines may include conjugate vaccines that could interact with other diphtheria-tetanus containing vaccines. Thus, the immune response of Neisseria meningitidis serogroup W (MenW) to the quadrivalent meningococcal conjugate vaccine (conjugated to
cross-reacting material 197 (CRM\textsubscript{197})) one month after being administered concurrently with, or 3-4 weeks prior to, or following combination tetanus, diphtheria and acellular pertussis vaccine (Tdap) was evaluated in a randomised controlled trial among Hajj pilgrims. The trial found that concurrent or sequential administration of Tdap and \textit{Neisseria meningitidis} serogroups A, C, W and Y (MenACWY) CRM\textsubscript{197} conjugate vaccine did not have a significant effect on the MenW immune response.

While gradual waning of immune response, particularly following early childhood immunisations have been observed extensively and investigated, however, an exceptional phenomenon of a natural rise in immune responses has also been noted but not previously investigated. Thus, a secondary analysis of available data on changes over several years to the immune response to meningococcal serogroup C conjugate vaccines among children vaccinated in early childhood was undertaken. This analysis found that a substantial minority (~15%) of children had a rise in their bactericidal antibody titers in the absence of a booster dose of vaccine. This may be attributed to a potential carriage-induced booster response and hence raises concerns that herd immunity is not as well-maintained as previously thought.
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<thead>
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<th>Abbreviations</th>
<th>Explanation</th>
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<tbody>
<tr>
<td>ACIP</td>
<td>Advisory Committee on Immunization Practice</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>ATP</td>
<td>According-to-protocol</td>
</tr>
<tr>
<td>AU</td>
<td>Australia</td>
</tr>
<tr>
<td>BICSL</td>
<td>Basic Infection Control Skills License</td>
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<tr>
<td>CAN</td>
<td>Canada</td>
</tr>
<tr>
<td>CFR</td>
<td>Case fatality rate</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CIES</td>
<td>Carrier induced epitopic suppression</td>
</tr>
<tr>
<td>CRM&lt;sub&gt;197&lt;/sub&gt;/CRM</td>
<td>Cross-reacting material 197</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>DT</td>
<td>Diphtheria toxoid</td>
</tr>
<tr>
<td>DTP</td>
<td>Diphtheria, tetanus and pertussis</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>GMAI</td>
<td>Geometric mean avidity index</td>
</tr>
<tr>
<td>GMT</td>
<td>Geometric mean titer</td>
</tr>
<tr>
<td>GSK</td>
<td>GlaxoSmithKline Biologicals</td>
</tr>
<tr>
<td>HCWs</td>
<td>Healthcare workers</td>
</tr>
<tr>
<td>Hib</td>
<td><em>Haemophilus influenzae</em> type B</td>
</tr>
<tr>
<td>Hib-MenCY-TT</td>
<td><em>Haemophilus influenzae</em> type b-<em>N. meningitidis</em> serogroups C and Y-tetanus-toxoid conjugate vaccine</td>
</tr>
<tr>
<td>HPA</td>
<td>Health Protection Agency</td>
</tr>
<tr>
<td>hSBA</td>
<td>Serum bactericidal assay using human complement</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>IMD</td>
<td>Invasive meningococcal disease</td>
</tr>
<tr>
<td>KSA</td>
<td>Kingdom of Saudi Arabia</td>
</tr>
<tr>
<td>MACP</td>
<td>Meningococcal serogroup A and C polysaccharide</td>
</tr>
<tr>
<td>MCC</td>
<td>Meningococcal serogroup C conjugate vaccine</td>
</tr>
<tr>
<td>MCV</td>
<td>Meningococcal conjugate vaccine</td>
</tr>
<tr>
<td>MCV4</td>
<td>Quadrivalent meningococcal conjugate vaccine</td>
</tr>
<tr>
<td>MD</td>
<td>Meningococcal disease</td>
</tr>
<tr>
<td>MenA</td>
<td><em>Neisseria meningitidis</em> serogroup A</td>
</tr>
<tr>
<td>MenACWY</td>
<td><em>Neisseria meningitidis</em> serogroups A, C, W and Y</td>
</tr>
<tr>
<td>MenACWY-C</td>
<td>Quadrivalent meningococcal serogroups A, C, W and Y conjugate vaccine</td>
</tr>
<tr>
<td>MenACWY-CRM&lt;sub&gt;197&lt;/sub&gt;</td>
<td>Quadrivalent MenACWY CRM&lt;sub&gt;197&lt;/sub&gt; conjugate meningococcal vaccine</td>
</tr>
<tr>
<td>MenACWY-PS</td>
<td>Quadrivalent meningococcal serogroups A, C, W and Y polysaccharide vaccine</td>
</tr>
<tr>
<td>MenB</td>
<td><em>Neisseria meningitidis</em> serogroup B</td>
</tr>
<tr>
<td>MenB-4C</td>
<td>Four component MenB vaccine</td>
</tr>
<tr>
<td>MenB-FHbp</td>
<td>A factor H binding protein based MenB vaccine</td>
</tr>
<tr>
<td>MenC</td>
<td><em>Neisseria meningitidis</em> serogroup C</td>
</tr>
<tr>
<td>MenCV</td>
<td>Meningococcal serogroup C conjugate vaccine</td>
</tr>
<tr>
<td>MenW</td>
<td><em>Neisseria meningitidis</em> serogroup W</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
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</tr>
<tr>
<td>MenY</td>
<td><em>Neisseria meningitidis</em> serogroup Y</td>
</tr>
<tr>
<td>MG</td>
<td>Mass gathering</td>
</tr>
<tr>
<td>MLST</td>
<td>Multi-locus sequence typing</td>
</tr>
<tr>
<td>MMR</td>
<td>Measles, mumps and rubella</td>
</tr>
<tr>
<td>MoH</td>
<td>Ministry of Health</td>
</tr>
<tr>
<td>MPSV4</td>
<td>Quadrivalent MenACWY polysaccharide vaccine</td>
</tr>
<tr>
<td>NCIRS</td>
<td>National Centre for Immunisation Research and Surveillance</td>
</tr>
<tr>
<td>NIP</td>
<td>National Immunisation Program</td>
</tr>
<tr>
<td>NOS</td>
<td>Newcastle-Ottawa Scale</td>
</tr>
<tr>
<td>OMP</td>
<td>Outer membrane protein</td>
</tr>
<tr>
<td>OMPC</td>
<td>Outer membrane protein complex</td>
</tr>
<tr>
<td>OMV</td>
<td>Outer membrane vesicle</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>PCV</td>
<td>Pneumococcal conjugate vaccine</td>
</tr>
<tr>
<td>PCV-13</td>
<td>13 valent pneumococcal conjugate vaccine</td>
</tr>
<tr>
<td>PCV-7</td>
<td>7 valent pneumococcal conjugate vaccine</td>
</tr>
<tr>
<td>PHE</td>
<td>Public Health England</td>
</tr>
<tr>
<td>PP</td>
<td>Per protocol</td>
</tr>
<tr>
<td>PRISMA</td>
<td>Preferred reporting items for systematic reviews and meta-analyses</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>rSBA</td>
<td>Serum bactericidal assay using rabbit complement</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SBA</td>
<td>Serum bactericidal assay</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SE</td>
<td>Standard error</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for Social Sciences</td>
</tr>
<tr>
<td>ST</td>
<td>Sequence type</td>
</tr>
<tr>
<td>Tdap</td>
<td>Combination diphtheria, tetanus and acellular pertussis vaccine</td>
</tr>
<tr>
<td>TT</td>
<td>Tetanus toxoid</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>VE</td>
<td>Vaccine effectiveness</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</table>

Note: To comply with journal’s style two different glossaries—MCC and MenCV—have been used for meningococcal serogroup C conjugate vaccine.
INTRODUCTION

Meningococcal disease

Meningococcal disease is caused by Neisseria meningitidis (the meningococcus); a Gram-negative, aerobic encapsulated diplococcus [1, 2]. Thirteen serogroups of N. meningitidis have been identified, based on the polysaccharide capsule [3, 4], with six serogroups (namely A, B, C, W, X and Y) responsible for the majority of invasive meningococcal disease (IMD) cases [5].

The meningococcus is transmitted by direct contact with respiratory secretions, e.g. via coughing, and may asymptotically colonise the pharynx and upper respiratory tract or result in invasive disease [6, 7]. It is estimated that 1 in 10 people carry the organism without any symptoms (most commonly, older adolescents and young adults), known as asymptomatic pharyngeal carriage, and in rare cases it may invade across the pharyngeal mucosa into the bloodstream to cause IMD [8]. However, asymptomatic carriage is much more prevalent than invasive disease, and only about 1% of carriers develop IMD [2, 9].

N. meningitidis is a leading cause of serious epidemic or sporadic systemic bacterial infections, most commonly manifesting as purulent meningitis or septicaemia [10, 11], and it is the only bacterium that can cause large scale meningitis outbreaks [12]. There are an estimated 1.2 million worldwide cases of meningococcal disease every year, resulting in up to 135,000 fatalities [13]. Incidence of meningococcal disease varies globally, with annual rates reaching 230 per 100,000 in the African meningitis belt countries, and as low as 1 or 2 per 100,000 in developed countries [13]. The risk of meningococcal carriage and disease is
higher among particular age groups, certain community settings, travellers to some destinations and immune compromised individuals.

**Vulnerable populations**
The prevalence of IMD peaks during infancy and again, to a lesser extent, in late adolescence/early adulthood (those aged 15 through to 24 years) [11, 14]. Lack of immunity plays an important role in the increased prevalence of IMD in infancy. Although the overall prevalence among these age groups has decreased, in large part due to the introduction of vaccines, reduced prevalence of smoking and improved socio-economic conditions, the observation of waning of immune responses over time following early childhood vaccination remains a concern for resurgence of disease in adolescence [15-20]. The raised prevalence of IMD among adolescents and young adults is linked to the socio-behavioural characteristics of this age group which facilitate high rates of carriage and transmission of meningococci (the so-called “drivers of transmission”). Smoking and intimate kissing or engagement in closed and crowded environments i.e. attending crowded social settings, patronising bars or night clubs, and living in dormitories or residential halls are common features of this age group [21-25].

Closed and semi-closed community settings, namely university residential halls and military barracks, are associated with high rates of meningococcal transmission and carriage acquisition, and have experienced recurrent outbreaks of IMD [9, 26]. For instance, the risk for IMD is higher among college freshmen living in residential halls compared to other college students living off-campus, or teenagers and young adults who are not attending college. Outbreaks have also been reported in other crowded settings with inadequate sanitary conditions such as among refugees [27-29].
Travelling, including pilgrimage to Hajj, is yet another vulnerable circumstance. Attendance at the annual Hajj pilgrimage in Makkah, Saudi Arabia carries an amplified risk of meningococcal disease, and the Hajj is also linked to multiple intercontinental outbreaks [30, 31].

As such, vaccination is recommended for members of vulnerable groups in many countries and strategies such as mass or targeted vaccination programmes have been applied to control epidemics and endemic disease caused by *N. meningitidis* globally. Meningococcal vaccines are included in the National Immunisation Program in many developed countries [32]. University freshmen are also often recommended to receive the vaccine and at times are offered mass vaccination [32, 33]. Vaccination is a mandatory requirement for all pilgrims and seasonal workers attending Hajj or Umrah [34].

Other vulnerable populations include travellers to the “meningitis belt” in sub-Saharan Africa [35] and a variety of immune compromising conditions which will not be addressed with this thesis [36-39].

**Diagnosis and treatment**

The gold standard method for diagnosing meningococcal disease has been through isolation of the pathogen from sterile body fluids such as cerebrospinal fluid (CSF) or blood. However, a decreased sensitivity of culture is expected in pre-treated cases; early initiation of empiric antibiotic treatment is advised once meningococcal infection is suspected without waiting for laboratory confirmation [1, 2]. Polymerase chain reaction (PCR) can be used for identification of meningococci without the need for a viable organism [2, 40].

First line treatment is intravenous third generation cephalosporins (cefotaxime or ceftriaxone) [41-43], alternatively, ampicillin and penicillin may be used [10, 41, 42].
Additionally, many cases may require intensive supportive care in a fully equipped facility [7, 41]. Antimicrobial chemoprophylaxis is the primary approach for preventing secondary cases, and is used to control outbreaks alongside mass vaccination [44, 45].

**Prevention**

Social distancing (e.g. isolation measures), health education to minimise high risk behaviours, and vaccination are considered the main preventative measures to reduce the incidence of IMD; of which, prevention by vaccination is often the most practical and effective [46, 47]. Despite advances in and availability of highly effective antibiotics, IMD is still a potentially lethal condition with a case fatality ratio of about 10% in treated individuals [3]. Furthermore, despite advanced intensive care support in specialist centres, about 20% of survivors are left with long-term sequelae including hearing loss, neurological damage, scarring, memory loss and limb loss [8, 48-50].

Although the meningococcus remains a dreadful pathogen, tremendous approaches have been made to control it, including the development of effective vaccines. The meningococcal polysaccharide vaccine was first developed in 1960’s in response to IMD outbreaks within US military establishments [51, 52]. The use of vaccines against specific meningococcal serogroups causing the outbreaks led to a dramatic decline in IMD incidence [53]. Over time, the serogroups covered by the vaccines and advances in immune responsiveness due to vaccines has improved have expanded [54].
Meningococcal polysaccharide versus conjugated vaccines

While meningococcal polysaccharide vaccines have been successful in reducing the burden of disease, their efficacy is hindered by significant limitations [55, 56]. Plain polysaccharide vaccines do not elicit adequate immune response in young children or immune memory in any age group, because they stimulate mature B-cells but not T-cells (T cell-independent), and thus the initial antibody response wanes rapidly over time. There is also evidence that they may cause immune hyporesponsiveness, by which the immune response to following doses is lower than the initial response, mostly among children under two years of age and for serogroup C in particular [57, 58]. In addition, their effect on nasopharyngeal carriage is short-lived or negligible [12, 59] with no significant induction of herd protection. To overcome these limitations, a carrier protein, such as tetanus toxoid, is bound to the meningococcal capsular polysaccharide to produce the more immunogenic conjugate vaccines (Table 1) [60, 61]. The meningococcal conjugate vaccines surpass their polysaccharide counterparts by their ability to provoke both T and B lymphocyte-mediated responses and, hence, elicit an immune response and memory in most age groups [36]. They have increasingly replaced plain polysaccharide vaccines in many developed countries since the late 1990s. This ongoing replacement in addition to the growing number of available conjugate vaccines (for example, against Haemophilus influenzae type b and pneumococcal conjugate vaccines) raises concerns about immune interaction between conjugate vaccines themselves, or between their carrier proteins and other vaccines containing the same proteins as antigens [62]. This becomes important when multiple vaccines are required in a short period of time, e.g. for travellers, including Hajj pilgrims. Vaccination strategies should be planned judiciously in order to avoid interactions.
### Table 1. Characteristics of meningococcal plain polysaccharide versus protein-conjugate vaccines

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Polysaccharide</th>
<th>Conjugate</th>
</tr>
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<tbody>
<tr>
<td>Immunogenicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>High</td>
<td>Very High</td>
</tr>
<tr>
<td>Infants &lt;2 years</td>
<td>Poor</td>
<td>High</td>
</tr>
<tr>
<td>Quality of antibodies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avidity</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>SBA titers</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Response to booster</td>
<td>Poor</td>
<td>High</td>
</tr>
<tr>
<td>Induction of memory</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Reduction of pharyngeal colonisation</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Duration of protection</td>
<td>Shorter</td>
<td>Longer</td>
</tr>
</tbody>
</table>

**An overview marketed meningococcal vaccines**

Vaccines against *N. meningitidis* are based on the meningococcal capsular polysaccharide (against serogroups A, C, W and Y) or the outer membrane proteins and vesicles (against serogroup B). These include monovalent and multivalent polysaccharide and polysaccharide-protein conjugate vaccines (Table 2).
<table>
<thead>
<tr>
<th>Serogroup(s)</th>
<th>Formula</th>
<th>Type of vaccine</th>
<th>Brand</th>
<th>Licensed age group</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>MenA-TT</td>
<td>Conjugate</td>
<td>MenAfriVac</td>
<td>Africa: 3 months–29 years</td>
</tr>
<tr>
<td>B</td>
<td>MenB-FHbp</td>
<td>Recombinant protein</td>
<td>Trumenba</td>
<td>US: 10-25 years</td>
</tr>
<tr>
<td>B</td>
<td>MenB-4C</td>
<td>Recombinant protein</td>
<td>Bexsero</td>
<td>AU: ≥2 months</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td>CAN: 2 months–17 years</td>
</tr>
<tr>
<td>C</td>
<td>MCC-TT</td>
<td>Conjugate</td>
<td>NeisVac-C</td>
<td>AU: ≥8 weeks</td>
</tr>
<tr>
<td>C</td>
<td>MCC-TT/Hib-TT</td>
<td>Combination, conjugate</td>
<td>Menitorix</td>
<td>CAN: ≥2 months</td>
</tr>
<tr>
<td>C</td>
<td>MCC-CRM&lt;sub&gt;197&lt;/sub&gt;</td>
<td>Conjugate</td>
<td>Menjugate</td>
<td>UK: ≥2 months–2 years</td>
</tr>
<tr>
<td>C</td>
<td>MCC-CRM&lt;sub&gt;197&lt;/sub&gt;</td>
<td>Conjugate</td>
<td>Meningitec</td>
<td>AU: ≥6 weeks</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td>CAN: ≥2 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>UK: ≥2 months</td>
</tr>
<tr>
<td>Bivalent C/W</td>
<td>Hib-MenCY-TT</td>
<td>Combination, conjugate</td>
<td>MenHibrix</td>
<td>US: 6 weeks–18 months</td>
</tr>
<tr>
<td>Quadrivalent A, C, W, Y</td>
<td>MenACWY-DT</td>
<td>Conjugate</td>
<td>Menactra</td>
<td>AU: 2-55 years*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CAN: 9 months–55 years*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>US: 9 months–55 years*</td>
</tr>
<tr>
<td></td>
<td>MenACWY-CRM</td>
<td>Conjugate</td>
<td>Menevo</td>
<td>AU: 11 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CAN: 2 months–55 years*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>UK: ≥ 2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>US: 2 months–55 years*</td>
</tr>
<tr>
<td></td>
<td>MenACWY-TT</td>
<td>Conjugate</td>
<td>Nimenrix</td>
<td>AU: 1–55 years*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CAN: 12 months–55 years*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>UK: ≥ 12 months</td>
</tr>
<tr>
<td></td>
<td>MPSV4</td>
<td>Polysaccharide</td>
<td>Menomune</td>
<td>AU: ≥2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CAN: ≥2 years</td>
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<td></td>
<td></td>
<td></td>
<td>US: ≥ 2 years</td>
</tr>
<tr>
<td></td>
<td>MenACWY</td>
<td>Polysaccharide</td>
<td>Mencevax</td>
<td>AU: ≥2 years</td>
</tr>
<tr>
<td></td>
<td>MenACWY</td>
<td>Polysaccharide</td>
<td>ACWY Vax</td>
<td>UK: ≥2 years</td>
</tr>
</tbody>
</table>

* Can be used for >55-year-olds according to national guideline suggestions.
**Aims and objectives**

IMD is largely a vaccine preventable disease, and hence, immunisation is the key to prevent and control its burden. Therefore, it stands to reason that this thesis revolves around vaccines or circumstances that mandate it.

The gradual switch from monovalent to quadrivalent and from polysaccharide to conjugate vaccines has so far ensured a low disease incidence among vulnerable populations in many parts of the world. Nevertheless, the disease remains uncontrolled in other parts, and in specific situations and cases (sporadic and outbreak) continue to occur.

To this end, the purpose of this thesis is to explore ways to better protect vulnerable populations, focusing on vaccination coverage in settings where a mandatory vaccination policy is in place, understanding the effect of vaccination on meningococcal carriage, and interpretation of the immune interactions between vaccines and changes to the immune response over time following vaccination.

This thesis considers the annual Hajj pilgrimage as an exceptional opportunity to achieve its aims. The history of IMD in the Hajj dates back to 1987; furthermore, being an annual event and involving people from all around the globe, including visitors from the African meningitis belt, as well as the associated long lasting annual global meningococcal vaccination campaigns, have contributed to build up such consideration. Moreover, the context of the Hajj case could comprise two groups of at risk individuals: travellers and those within a closed population. The thesis also considered the young population who are also at increased risk of disease in that it explores the issue of waning of immune responses over years following early childhood immunisations.
The specific objectives of the works included in this thesis are:

1. To assess adherence to the pre-Hajj meningococcal vaccination policy and factors that affect uptake.

2. To assess the impact of MenACWY-C versus MenACWY-PS on nasopharyngeal carriage among Hajj pilgrims.

3. To explore the interaction between meningococcal conjugate vaccines and other vaccines.

4. To interpret changes in the immune responses to MCC over years following early childhood vaccination.

Structure of this thesis

The thesis is composed of four sections; (A) literature review, (B) cross-sectional surveys, (C) clinical trials, (D) summary and conclusion. Section A includes three publications: two systematic reviews and a book chapter presented in two chapters. Section B and C are represented in four chapters and composed of three original publications, one letter, one original survey currently in pre-submission stage, and one unpublished RCT (Figure 1).

Section A: Literature reviews

Chapter 1: Meningococcal Carriage and Disease in Crowded Settings, Hajj, Umrah and Other Mass Gatherings

Publication #1 | Systematic review:


This systematic review has been published in Vaccine and aimed to synthesise the currently available data on IMD (including outbreaks) in crowded closed and semi-closed settings other than Hajj and Umra to assess the burden of disease, and to improve understanding of risk factors and potential prevention and control strategies.
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SECTION A</strong> LITERATURE REVIEW</td>
<td>Chapter 1</td>
<td>Meningococcal disease burden and transmission in crowded settings and mass gatherings other than Hajj and Umrah: A systematic review</td>
</tr>
<tr>
<td></td>
<td>Publication #1</td>
<td>Meningococcal disease burden and transmission in crowded settings and mass gatherings other than Hajj and Umrah: A systematic review</td>
</tr>
<tr>
<td></td>
<td><strong>OVERVIEW</strong></td>
<td>Assessment of the burden of IMD in crowded and semi-closed settings (other than Hajj and Umrah) to enhance understanding of risk factors and potential prevention strategies</td>
</tr>
<tr>
<td></td>
<td>Chapter 2</td>
<td>Immunology of MCC</td>
</tr>
<tr>
<td></td>
<td>Publication #2</td>
<td>Meningococcal disease at Hajj, Umrah and other mass gatherings</td>
</tr>
<tr>
<td></td>
<td><strong>OVERVIEW</strong></td>
<td>Overview on the history, epidemiology and burden of meningococcal carriage and disease among Hajj and Umrah pilgrims</td>
</tr>
<tr>
<td></td>
<td>Chapter 3</td>
<td>Vaccine uptake and influencing factors</td>
</tr>
<tr>
<td></td>
<td>Publication #3</td>
<td>Update on the use of meningococcal serogroup C CRM_{197} conjugate vaccine (Meningitec) against meningitis</td>
</tr>
<tr>
<td></td>
<td><strong>OVERVIEW</strong></td>
<td>Exploring the immunological profile of different MenC conjugate vaccines to shed light on their divergent immunological performance</td>
</tr>
<tr>
<td></td>
<td>Chapter 4</td>
<td>Impact of MenACWY vaccine on carriage</td>
</tr>
<tr>
<td></td>
<td>Unpublished RCT</td>
<td>Impact of conjugate versus polysaccharide quadrivalent meningococcal (serogroup A, C, W &amp; Y) vaccine on meningococcal carriage among Hajj pilgrims</td>
</tr>
<tr>
<td></td>
<td><strong>OVERVIEW</strong></td>
<td>A RCT aimed primarily to compare the effects of conjugate versus polysaccharide quadrivalent meningococcal vaccine on nasopharyngeal carriage of meningococci mainly among domestic Hajj pilgrims</td>
</tr>
<tr>
<td></td>
<td>Chapter 5</td>
<td>MenACWY-C and immune interference</td>
</tr>
<tr>
<td></td>
<td>Publication #6&amp;7</td>
<td>Effect on MenW immunogenicity when Tdap was administered prior to, concurrent with, or subsequent to MenACWY CRM_{197} conjugate vaccine in adult Hajj pilgrims: A randomised controlled trial</td>
</tr>
<tr>
<td></td>
<td><strong>OVERVIEW</strong></td>
<td>A letter to the editor and a trial on the effect of Tdap vaccine on MenW when MenACWY CRM_{197} conjugate vaccine is administered concurrently or sequentially</td>
</tr>
<tr>
<td></td>
<td>Chapter 6</td>
<td>Pattern of immune response over years post priming with MCC</td>
</tr>
<tr>
<td></td>
<td>Publication #8</td>
<td>Evidence for rise in meningococcal serogroup C bactericidal antibody titers in the absence of booster vaccination in previously vaccinated children</td>
</tr>
<tr>
<td></td>
<td><strong>OVERVIEW</strong></td>
<td>A secondary analysis of data to explore pattern of changes in SBA titers of children who were followed for up to 10 years after being primed with MenC conjugate vaccine</td>
</tr>
</tbody>
</table>

**CRMs:** Diphtheria cross-reactive material; **IMD:** Invasive meningococcal disease; **MCC:** Meningococcal serogroup C conjugate vaccine; **MenACWY-C:** Quadrivalent meningococcal serogroups A, C, W and Y conjugate vaccine; **MenACWY-PS:** Quadrivalent meningococcal serogroups A, C, W and Y polysaccharide vaccine; **MenACWY:** *Neisseria meningitidis* serogroup A, C, W and Y; **MenC:** *Neisseria meningitidis* serogroup C; **MenW:** *Neisseria meningitidis* serogroup W; **RCT:** Randomised controlled trial; **SBA:** Serum bactericidal assay.
Publication #2 | Book chapter:
*corresponding and joint first author

This is a chapter in a book entitled “Healthcare in the Arab World” being published by Springer. This publication focuses on the epidemiology of meningococcal carriage and disease burden during Hajj and Umrah.

**Chapter 2: Immunogenicity, Immune Persistence and Induction of Immune Memory of MenC Conjugate Vaccines**

Publication #3 | Systematic review:

Considering that immunisation is a major contributor in controlling disease, this invited review deals with the immunology of the various conjugate vaccines. Since monovalent meningococcal serogroup C conjugate vaccines are well-studied, this systematic review examines the immunobiology of MenC conjugate vaccines (including MeningitecTM, MenjugateTM and NeisVac-C™) to understand the immunological profile of the different vaccines which may shed light on their divergent immunological performance.

**SECTION B: CROSS-SECTIONAL SURVEYS**

**Chapter 3: Vaccine Uptake and Factors that Affect it**

This section explored vaccine uptake plus its facilitators and barriers among two key groups at Hajj: domestic pilgrims and health care workers.
Since 2002, both domestic and overseas pilgrims are required to receive the quadrivalent meningococcal vaccine. There are several reports on meningococcal vaccine uptake among overseas pilgrims. However, data on vaccine uptake among domestic pilgrims (from within Saudi Arabia) remain scarce even though they form 35%-50% of Hajj pilgrims. This survey aimed to assess vaccine uptake among domestic pilgrims and to identify its predictors, facilitators and barriers.

**Publication #5 | Original research:**


All workers during Hajj, including health care workers, are required to be vaccinated against *N. meningitidis*. Providing health care service during Hajj involves increased risks of exposure and ensuring optimum vaccine coverage among health care workers is important to protect them and those who they are taking care of. Meningococcal vaccine is funded for health care workers in Saudi Arabia, however uptake at Hajj is suboptimal and factors affecting uptake are not fully understood. This cross-sectional survey aimed to evaluate uptake of meningococcal, influenza and pneumococcal vaccines, and to explore key factors affecting the vaccination rate among health care workers who served during the Hajj seasons of 2015-2017.
SECTION C: CLINICAL TRIALS

Chapter 4: Impact of quadrivalent meningococcal ACWY vaccines on meningococcal carriage

Unpublished RCT | Original research (submitted to the Journal of Travel Medicine):

Impact of quadrivalent meningococcal ACWY vaccines on meningococcal carriage among Hajj pilgrims: A randomised trial

The previous chapter demonstrated suboptimal vaccination coverage among both key domestic groups (pilgrims and health care workers). One possible way to compensate for this is to assess and, if possible, limit meningococcal carriage (ie induce sufficient herd immunity). The conjugate vaccines are believed to be capable of reducing carriage but no head to head trial has been conducted to compare this with polysaccharide vaccines. This chapter reports on the results of a randomised controlled trial aimed primarily to compare the effects of conjugate versus polysaccharide meningococcal quadrivalent ACWY vaccine on nasopharyngeal carriage 1-60 days after Hajj among mostly domestic Hajj pilgrims, and secondarily to assess meningococcal carriage before and after Hajj.

Chapter 5: Meningococcal Conjugate Vaccines and Immune Interference

Publication #6 | Letter to the editor:


Multiple vaccine administrations raise many concerns including augmentation of adverse events, impacts on compliance and most importantly the potential interaction/interference between vaccines and vaccine components. This letter discusses the potential interaction of
meningococcal conjugate vaccines with other vaccines containing the same carrier protein upon concurrent and/or sequential administration.

**Publication #7 | Original research:**

Tashani M, **Badahdah AM**, Alfelali M, Barasheed O, Alqahtani AS, Heron L, Wong M, Louth J, Rashid H, Borrow R, Booy R. Effect on meningococcal serogroup W immunogenicity when Tdap was administered prior, concurrent or subsequent to the quadrivalent (ACWY) meningococcal CRM(197)-conjugate vaccine in adult Hajj pilgrims: A randomised controlled trial. Vaccine. 2019 Jun 12;37(27):3562-3567.

This publication presents the outcomes of an RCT on the effect of Tdap (Boostrix®) vaccine on immunogenicity of CRM197-conjugated quadrivalent A, C, W, and Y meningococcal vaccine (Menveo®) when administered concurrently or sequentially.

**Chapter 6: Patterns of Immune Response over Years following Vaccination with Meningococcal Conjugate Vaccines**

**Publication #8 | Original research:**


This is a secondary data analysis of bactericidal antibody titers in children that were followed for up to 10 years after being primed with MenC conjugate vaccine in early childhood to delineate the different patterns of change in their bactericidal antibody titers and explore whether natural boosting may occur independent of vaccination.
SECTION A: LITERATURE REVIEWS

Chapter 1: Meningococcal Carriage and Disease in Crowded Settings; Hajj, Umrah and other Mass Gatherings

1.1 Meningococcal carriage in closed and semi-closed populations

Since acquisition of the meningococcus occurs through large respiratory droplets, a crowded setting with multiple direct close contacts provides an ideal environment for its spread. Closed and semi-closed populations such as college students, military recruits and multi-person households have the highest rate of meningococcal carriage [63-68]. The most recent meningococcal carriage findings in key closed and semi-closed populations, university students and military recruits, are summarised in the following table (Table 3).
<table>
<thead>
<tr>
<th>Year</th>
<th>Study design</th>
<th>Country</th>
<th>Number of swabs</th>
<th>Ages (years)</th>
<th>Overall carriage (%)</th>
<th>Identified serogroup(s)</th>
<th>Absent serogroup(s)</th>
<th>Not reported/not tested for</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013 [70]</td>
<td>Cross-sectional</td>
<td>Poland</td>
<td>559</td>
<td>21-52</td>
<td>5.7</td>
<td>B, C &amp; Y</td>
<td>A &amp; W</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2nd: 434</td>
<td></td>
<td>13.8</td>
<td>B, W &amp; X</td>
<td>A, C &amp; Y</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3rd: 443</td>
<td></td>
<td>12.6</td>
<td>B, C, W &amp; X</td>
<td>A &amp; Y</td>
<td>-</td>
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<td>4th: 443</td>
<td></td>
<td>5.2</td>
<td>B, C &amp; W</td>
<td>A, X &amp; Y</td>
<td>-</td>
</tr>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Carriage prevalence among university students</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
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<td>2nd: 91</td>
<td></td>
<td>51</td>
<td>B, C, &amp; Y</td>
<td>A, W &amp; X</td>
<td>-</td>
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<td>3rd: 74</td>
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<td>55</td>
<td>B, C, &amp; Y</td>
<td>A, W &amp; X</td>
<td>-</td>
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<tr>
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<td></td>
<td></td>
<td>4th: 63</td>
<td></td>
<td>62</td>
<td>B, C, W &amp; Y</td>
<td>A &amp; X</td>
<td>-</td>
</tr>
<tr>
<td>2009 [74]</td>
<td>Cross-sectional</td>
<td>Republic of Korea</td>
<td>1st: 136</td>
<td>ND</td>
<td>11.8</td>
<td>B &amp; C</td>
<td>A, W, X &amp; Y</td>
<td>-</td>
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<td>14.1</td>
<td>B, C, &amp; W</td>
<td>A, X &amp; Y</td>
<td>-</td>
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<tr>
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<td>2nd: 1049</td>
<td></td>
<td>46.3</td>
<td>B &amp; Y</td>
<td>-</td>
<td>A, C, W &amp; X</td>
</tr>
<tr>
<td>Year</td>
<td>Type</td>
<td>Country</td>
<td>Code</td>
<td>Sex</td>
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<td>-----------------------</td>
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<td>-------</td>
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<tr>
<td>2012</td>
<td>Cross-sectional</td>
<td>Chile</td>
<td>500</td>
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<td>B &amp; W</td>
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<td>1.5</td>
<td>B</td>
<td>A, C, W &amp; Y</td>
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<td>Cross-sectional</td>
<td>Nigeria</td>
<td>336</td>
<td>ND</td>
<td>ND</td>
<td>5.1</td>
<td>A, C, W, &amp; Y</td>
<td>-</td>
</tr>
<tr>
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<td>Cross-sectional</td>
<td>USA</td>
<td>1st: 1067</td>
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<td>18-26</td>
<td>12.8</td>
<td>B, C, X &amp; Y</td>
<td>A &amp; W</td>
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<td>2nd: 761</td>
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<td></td>
<td>14.6</td>
<td>B, C, X &amp; Y</td>
<td>A &amp; W</td>
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<td>17.1</td>
<td>B, C, X &amp; Y</td>
<td>A &amp; W</td>
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<td>3rd: 1045</td>
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<td>B, C &amp; Y</td>
<td>A, W &amp; X</td>
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<td>2nd: 878</td>
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<td>B, C, X &amp; Y</td>
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<td>20.8</td>
<td>B, W, X &amp; Y</td>
<td>A &amp; C</td>
</tr>
<tr>
<td>2015–16</td>
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<td>England</td>
<td>1st: 769</td>
<td>ND</td>
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<td>14.3</td>
<td>B, W, &amp; Y</td>
<td>-</td>
</tr>
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<td>B, W, &amp; Y</td>
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<td>B, W, &amp; Y</td>
<td>-</td>
</tr>
</tbody>
</table>

ND, not documented; (-) nil
1.2 Meningococcal disease in closed and semi-closed populations

Review

Meningococcal disease burden and transmission in crowded settings and mass gatherings other than Hajj/Umrah: A systematic review

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Abstract

Background: Mass gatherings (MGs) such as the Hajj and Umrah pilgrimages are known to amplify the risk of invasive meningococcal disease (IMD) due to enhanced transmission of the organism between attendees. The burden of IMD at MGs other than Hajj and Umrah has not previously been quantified through a systematic review.

Methods: A systematic search for relevant articles in PubMed and Embase was conducted using MeSH terms; this was buttressed by hand searching. Following data abstraction, a narrative synthesis was conducted to quantify the burden of IMD at MGs and identify potential risk factors and mitigation measures.

Results: Thirteen studies reporting occurrence of IMD at MGs or similar crowded settings were identified. Eight studies reported cases or outbreaks in MGs of >1000 people; five others reported IMD in other crowded settings; all occurred between 1991 and 2015. All age groups were involved in the identified studies; however the majority of cases (>80%) were young people aged 15–24 years. The number of affected people ranged from one to 321 cases and the overall crude estimate of incidence was calculated as 66 per 100,000 individuals. Serogroups A, C, B and W were identified, with serogroups A and C being most common. Of 450 cases of IMD reported in non-Hajj/Umrah MGs, 67 (14.9%) had fatal outcomes.

Conclusion: IMD outbreaks at non-Hajj/Umrah MGs are generally much smaller than Hajj-related outbreaks and affect mainly young people. Health education and vaccination should be considered for attendees of high risk non-Hajj/Umrah MGs, especially those involving adolescents and young adults.

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1. Introduction

*Neisseria meningitidis* is an important cause of sepsis and meningitis worldwide [1], and is associated with a considerable case fatality rate (CFR) in spite of treatment [2,3]. It is the only pathogen linked to epidemics of bacterial meningitis and each year approximately 1.2 million cases of invasive meningococcal disease (IMD) are reported globally, of which around 135,000 succumb to the illness [4,5]. IMD remains a major global public health issue, with most cases being caused by serogroups A, B, C, W, Y and X [1]. Elevated rates of IMD among military servicemen in the United States of America (USA) during the 1960s inspired the development of meningococcal polysaccharide vaccines [6]. Subsequently, more immunogenic polysaccharide-conjugate vaccines were developed against most serogroups that cause disease; however, global uptake has been slow and limited and sporadic cases and outbreaks continue to occur, particularly in crowded settings and mass gatherings (MGs) [7–9].

MGs are characterised by a large congregation of people in a specific geographic area, over a defined duration, for a specific purpose [10]. The number of participants attending, as well as the location, frequency and duration of the event may vary according to the type of MG. Generally, the minimum number of attendees required for an event to qualify as a MG is 1000 people [10]. The event may be a one-time occurrence (e.g., a state funeral), an annual gathering (e.g., Hajj) or one that occurs less often (e.g., the Olympic Games). The congregations may last for weeks (e.g., Kumbh Mela) or just a few hours (e.g., a sporting fixture). Furthermore, the degree of organisation and monitoring, and thus the ability to protect the health and safety of attendees, also varies, from very detailed management of the event (e.g., the Olympic Games) to more informal oversight (e.g., music festivals). Despite the heterogeneity of these events, close contact between a large number of individuals from diverse backgrounds is the hallmark of all MGs, and the risk of transmission of communicable diseases [11] including IMD [12] amplifies during such events.

Additionally, shared accommodation, compromised hygiene and other high risk behaviours (e.g., smoking, intimate kissing) increase the risk of outbreaks of IMD at MGs [13,14]. For example, two large intercontinental outbreaks of IMD have occurred in the past due to Hajj, an annual assembly of more than two million Muslims in Makkah. The first, in 1987, affected around two thousand pilgrims [15]; and in 2000–2001 a second outbreak affected over 2400 individuals across the world [16]. These have been well-reported elsewhere and the subject of several excellent reviews [17–19]. Meningococcal outbreaks have occurred in other MGs or crowded settings, but have not previously been systematically reviewed. To address this, this review aims to synthesise the currently available data on IMD (including outbreaks) in non-Hajj/Umrah MGs to assess the burden of disease and to enhance understanding of risk factors and potential prevention and control strategies.

2. Methods

2.1. Search strategy

A search was undertaken through Medline and Embase using the following search terms: ‘meningococcal’, ‘meningitis’ and ‘*Neisseria meningitidis*’ with a combination of keywords and terms associated with MGs including ‘mass gathering’, ‘gathering’, ‘crowd’, ‘camp’, ‘championship’, ‘sport’, ‘Olympics’, ‘FIFA’, ‘EURO’, ‘concert’, ‘festival’, ‘pilgrimage’, ‘nursing home’, and ‘travel’. Publications in all potential languages from database inception to 31 August 2016 were retrieved. A manual search was also performed to identify additional relevant papers from reference lists of identified studies.

2.2. Study selection

Two reviewers (AB, HR) independently selected studies for inclusion while other authors (RB, AK) arbitrated when a discrepancy occurred. Mendeley was used to identify and delete duplicate records [20]. Any original manuscript published in English that described the occurrence of IMD in any MG or crowded setting was included. Articles related to IMD occurring at Hajj or Umrah or those related to asymptomatic carriage or to non-meningococcal meningitis were excluded. For the purpose of this review we included any publications describing meningococcal outbreaks in an event attended by 1000 or more people. Publications reporting IMD outbreaks in crowded settings of ≥1000 individuals (such as university residential halls, military barracks, cruise ships and large dance parties) were also included to help better understand the transmission and epidemiology of IMD during MGs. The ‘preferred reporting items for systematic reviews and meta-analyses (PRISMA)’ statement was used to guide and report the search methodology.

2.3. Data extraction

The following data (if available) were extracted from each article: setting of outbreak, place, year, duration, number of attendees/affected population, number of cases, age group, fatalities, serogroups responsible and control measures undertaken.

2.4. Quality assessment

To evaluate data quality, the Newcastle-Ottawa Scale (NOS) for cross-sectional and cohort studies ([http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)) was used. Two authors (AB, HR) independently evaluated the quality of included studies; any disagreement was resolved through consensus.
3. Results

3.1. Study characteristics

Fig. 1 outlines the number of articles identified. After removal of duplicates and exclusion of non-relevant articles, 13 studies were included in the review (Table 1). A total of eight studies reported cases or outbreaks of IMD in typical MGs other than Hajj/Umrah, and five others in crowded settings resembling MGs of at least 1000 individuals (university residence halls, military base and a dance party). The reported outbreaks occurred between 1991 and 2015. Seven (54%) outbreaks were reported during events held in Europe (four in the United Kingdom [UK]), two (15%) in the Americas, two (15%) in Asia, and two (15%) in Africa. The duration of the reported outbreaks was as short as two days for an outbreak linked to a rugby match in the UK in 2001 [9], and over a year for outbreaks at a university residential hall in the USA in 1991 [21,22] and a Sudanese refugee camp in Uganda in 1994 [23].

Due to heterogeneity in study design, outbreak settings, case ascertainment strategies and method of confirming diagnoses a narrative synthesis rather than a meta-analysis was performed. The overall quality of included studies was modest (Table 2) with mean and median NOS scores of 5 out of maximum 9 for case-controlled studies (1) and maximum 10 for cross-sectional studies (12).

3.2. Affected age groups

Four outbreaks (two in university residential halls and two at youth events) were limited to the 15–24-year age group [8,21,22,24,25]. Additionally, 50 out of 63 cases (79%) where individual ages were reported belonged to this age group. Only two outbreaks involved a wide range of age groups; both occurred in refugee camps [23,26,27].

3.3. Estimated incidence rate

In nine outbreaks the incidence rate was available or calculable [8,9,21,24,28-32]. Overall, the estimated incidence of IMD during the included MGs ranged from 21 (over 11 days) [8] to 1600 (over 3 days) [30] per 100,000 individuals. The crude overall estimate of incidence using available data from the included studies was 66 per 100,000 individuals over the variable durations of the included MGs.

3.4. Case fatality rate

Sixty-seven fatalities were reported among 450 cases of IMD, resulting in an overall CFR of 14.9%, among 11 outbreaks where fatalities were documented. The most deadly outbreak (CFR = 62%) occurred during a dance party in Brazil where 5/8 affected individuals died [31]. Another two outbreaks reported CFR of 50%: one linked to a university residential hall in the UK where 3/6 affected individuals died [25], and one to a rugby match where two deaths were reported among four cases in adults ≥50 years of age [9].

3.5. Distribution by serogroup

N. meningitidis serogroup C (MenC) was isolated in seven outbreaks (54%), serogroup A (MenA) in three outbreaks (23%), and...
<table>
<thead>
<tr>
<th>Year</th>
<th>Place and setting of outbreak</th>
<th>Duration of outbreak</th>
<th>Number of attendees/affected population</th>
<th>Number of cases (n)/method of diagnosis</th>
<th>Age of cases</th>
<th>Fatalities</th>
<th>Microbiological details</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>University residential hall, Illinois, USA [21,22]</td>
<td>February 1991 to April 1992</td>
<td>25,000</td>
<td>n = 9 (including 1 at a nearby college); 2 by blood and CSF culture, 6 by blood culture only, 1 by serum latex agglutination.</td>
<td>18–22 years</td>
<td>3</td>
<td>8 MenC</td>
<td>- 7 cases had patronised campus bar 1–2 weeks prior to illness - Outbreak was associated with patronage of one particular bar (p = 0.0006; odds ratio = 23.1, 95% confidence interval 3.0–571.5) - Approximately 16,000 students were vaccinated using a combined serogroup A, C, Y, and W meningococcal polysaccharide vaccine in February 1992 - An isolation ward was opened in the Health Centre at Ogbue for treatment of meningitis cases - Mass immunisation campaign started 8 days after identification of the index case</td>
</tr>
<tr>
<td>1994</td>
<td>Sudanese refugee camp, Moyo District, Northern Uganda. [23]</td>
<td>February 22, 1994 to March 1995</td>
<td>96,860 (averaged over the year)</td>
<td>n = 321 (291 refugees, 30 local residents)</td>
<td>&lt;1–45+ years</td>
<td>43</td>
<td>4 CSF samples confirmed MenA, type 21:P1.9, clone III-1</td>
<td>- Isolation of patients in a separate tent - Immunization was delayed due to vaccine shortage. Mass vaccination undertaken one month after identification of the index case</td>
</tr>
<tr>
<td>1994</td>
<td>Rwandan refugee camp, Goma, Zaire [26,27]</td>
<td>July and August 1994</td>
<td>260,000</td>
<td>n = 65</td>
<td>13.4 ± 1.4 years</td>
<td>6</td>
<td>All confirmed cases due to MenA</td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>International youth football tournament, Belgium [28]</td>
<td>May 9 to December 24, 1997</td>
<td>1300 participants from 4 countries</td>
<td>n = 11</td>
<td>All by blood culture.</td>
<td>12–39 years</td>
<td>1</td>
<td>All MenC, ET35, phenotype 2a: P1.5</td>
</tr>
<tr>
<td>1997</td>
<td>University halls of residence, Southampton, UK [25]</td>
<td>3-week period in October 1997</td>
<td>&gt;1160 residents (4460 at-risk individuals including students and staff living or working in halls of residence and all first-year students)</td>
<td>n = 6</td>
<td>3 by culture of blood (2) or CSF (1), 2 by PCR of blood or CSF, 1 clinical diagnosis.</td>
<td>18–19 years</td>
<td>3</td>
<td>All MenC, ST11, serotype 2a, porA genotype P1.5, P1.2</td>
</tr>
<tr>
<td>2001</td>
<td>Rugby match, UK [9]</td>
<td>January 10 and 11, 2001</td>
<td>7602</td>
<td>n = 4</td>
<td>All by blood culture.</td>
<td>50–59 years</td>
<td>2</td>
<td>All MenC, ST11, serotype 2a, porA genotype P1.5, P1.2</td>
</tr>
<tr>
<td>2006</td>
<td>Military barracks, India [29]</td>
<td>February 1 to May 26, 2006</td>
<td>2976 residents of the barracks</td>
<td>n = 17 (6 resident in the barracks, 15 were young soldiers)</td>
<td>21–26 years (15 known cases)</td>
<td>2</td>
<td>MenA</td>
<td>- 2976 troops living in accommodation designed for 2227 troops - Vaccines not available for mass immunisation</td>
</tr>
<tr>
<td>2006</td>
<td>Army barracks, Skwierzyna, Poland [30]</td>
<td>March 22 to 24, 2006</td>
<td>250 (outbreak sub-unit)</td>
<td>n = 4</td>
<td>All by culture of blood or CSF</td>
<td>ND</td>
<td>0</td>
<td>All MenC, ST11/ET37 with identical PFGE</td>
</tr>
<tr>
<td>Year</td>
<td>Place and setting of outbreak</td>
<td>Duration of outbreak</td>
<td>Number of attendees/affected population</td>
<td>Number of cases (n)/method of diagnosis</td>
<td>Age of cases</td>
<td>Fatalities</td>
<td>Microbiological details</td>
<td>Additional comments</td>
</tr>
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</tr>
<tr>
<td>2007</td>
<td>European Youth Olympic Sports Festival, Northern Aragon, Spain [24]</td>
<td>February 21, 2007</td>
<td>1500 athletes from 43 countries</td>
<td>n = 1 By CSF culture</td>
<td>16 years</td>
<td>0</td>
<td>MenB</td>
<td>- Chemoprophylaxis was extended to all residents of the unit (n = 1300) including civil personnel after strain was confirmed - Movement of soldiers within and outside the army unit was restricted between 21 March and 4 April</td>
</tr>
<tr>
<td>2009</td>
<td>Dance party, Trancoso, Brazil [31]</td>
<td>October 21–26, 2009</td>
<td>1000</td>
<td>n = 9 5 by blood or CSF culture, 4 by detection of MenC antigen in CSF by latex agglutination.</td>
<td>14–39 years</td>
<td>6</td>
<td>All MenC, phenotype 23: P1.5, ST3780, within 92% relatedness on PFGE</td>
<td>- One case was not linked to the party</td>
</tr>
<tr>
<td>2012</td>
<td>Cruise ship, Italian coast [32]</td>
<td>October 2012</td>
<td>2000</td>
<td>n = 4 All by CSF culture</td>
<td>26–47 years</td>
<td>1</td>
<td>All MenC, ST11, genotype P1.5–1,10–8:F3-6</td>
<td>- Alert announced from Maritime Port Health Offices of Livorno to the Ministry of Health - Ciprofloxacin chemoprophylaxis administered to all individuals present on the ship</td>
</tr>
<tr>
<td>2015</td>
<td>World Scout Jamboree, Yamaguchi, Japan [8]</td>
<td>August 8 to 19, 2015</td>
<td>33,000 scouts from 162 countries.</td>
<td>n = 8 4 confirmed cases from UK: method of diagnosis not reported. 1 confirmed (by PCR and culture in blood and CSF) and 3 suspected cases from Sweden.</td>
<td>15–24 years (Swedish cases); unknown for UK cases</td>
<td>ND</td>
<td>2 MenW from 4 UK cases</td>
<td>UK: One case was a household contact of a scout; the other 3 cases were in the same scout group and returned to Scotland on 8 August - ‘Advise and inform’ letter sent by Health Protection Scotland to all participants from UK and from Swedish public health authorities to participants from Sweden</td>
</tr>
</tbody>
</table>

serogroups B (MenB) [24] and W (MenW) [8] in one each. Serogroup data were not available for one outbreak [12] (Table 3).

3.6. Distribution by setting

Four studies reported outbreaks in closed residence settings: two in university accommodation (in the USA [21,22] and UK [25]), and two in military housing (in Poland [30] and India [29]). Three other studies reported outbreaks in camp settings, including two large outbreaks in refugee camps in Africa (Northern Uganda [23] and Zaire [26,27]) and one at an international youth scout camp in Japan [8]. Four studies described outbreaks linked to a sports event, all occurring in Europe [9,12,24,28]. One outbreak was linked to a dance party in Brazil [31] and another occurred on a cruise ship sailing the Italian coast [32].

3.7. Control and preventive measures

Extended outbreak management strategies (beyond contact tracing and offering chemoprophylaxis to close contacts) were reported during six outbreaks. Mass immunisation was utilised during two large outbreaks of MenA disease occurring in refugee camps in Uganda and Zaire in 1994 [23,26,27] as well as during two outbreaks of MenC disease occurring in university halls of residence in the USA (1991–1992) and UK (1997) [21,22,25]. In these immunisation campaigns, the target populations included between 4500 and 260,000 individuals. Mass chemoprophylaxis was provided to all exposed populations (~1300–4500 individuals) during outbreaks of MenC disease in a military barracks in Poland [30], a university halls of residence in the UK [25] and on a cruise ship [32]. Due to a lack of vaccine supply, mass immunisation was not undertaken during an outbreak of MenA disease at a military base in India [29]. Further isolation measures and restrictions on movement were utilised during the two reported outbreaks of MenA disease in refugee camps [23,26,27], as well as the Polish military barracks outbreak [30].

3.8. Carriage studies

Carriage studies using throat swabs were conducted during four outbreaks that occurred in semi-closed crowded settings (military barracks and university residential halls) [21,22,25,29,30]. Overall, carriage of N. meningitidis was identified in 14 (14.4%) out of 97 randomly selected soldiers in a military barracks in India following an outbreak of MenA disease affecting 17 individuals (15 soldiers) [29]. During a MenC outbreak in a Polish army unit six (10%) out of 61 roommates of affected soldiers carried a meningococcal strain identical to the outbreak strain; whereas the outbreak strain was not isolated from any other residents of the military base (population 1300) [30]. In a university setting outbreak, overall carriage rate of meningococci was 25% (147/587) among undergraduates, of whom 3.4% carried MenC (0.9% of total undergraduate population investigated), however no carriers of the outbreak strain were identified [25]. In a similar outbreak in the USA, carriage rate of

### Table 2
Newcastle and Ottawa Scale (NOS) scores for included studies.

<table>
<thead>
<tr>
<th>Case-control studies</th>
<th>Selection</th>
<th>Comparability</th>
<th>Exposure</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imrey et al. [22]</td>
<td>***</td>
<td>–</td>
<td>**</td>
<td>5</td>
</tr>
</tbody>
</table>

### Table 3
Serogroups responsible for reported outbreaks in non-Hajj/Ummrah mass gatherings.

<table>
<thead>
<tr>
<th>Serogroup</th>
<th>Year</th>
<th>Place</th>
<th>Setting</th>
<th>Ages of affected individuals</th>
<th>Number of reported Outbreaks</th>
</tr>
</thead>
<tbody>
<tr>
<td>MenA</td>
<td>1994, 2006</td>
<td>India, Uganda, Zaire</td>
<td>Refugee camp, military barracks</td>
<td>All age groups</td>
<td>3 [23,26,27,29]</td>
</tr>
<tr>
<td>MenB</td>
<td>2007</td>
<td>USA, UK, Belgium, Denmark, Germany, Netherlands, Poland, Brazil, Italy</td>
<td>University residential halls, sports events, military barracks, dance party, cruise ship</td>
<td>16</td>
<td>1 [24]</td>
</tr>
<tr>
<td>MenC</td>
<td>2015</td>
<td>UK</td>
<td>World Scout Jamboree</td>
<td>12–59</td>
<td>7 [9,21,22,25,28,30-32]</td>
</tr>
</tbody>
</table>

meningococci was higher among predominantly student bars workers than university health centre clients: 38% versus 10% for all meningococci, 4.7% versus 0.3% for MenC carriage, and 3.5% versus 0.2% for the outbreak strains respectively [21,22].

4. Discussion

This systematic review confirms that IMD outbreaks occur in non-Hajj/Umrah MGs and in crowded settings of >1000 individuals, including, but not limited to, university halls, military establishments, camps and sport events that are mostly attended by young adults. Refugees, university freshmen and military recruits are the most commonly affected groups. Meningococcal serogroups A, B, C, and W have all been attributed to outbreaks, although the majority of published reports refer to disease caused by MenC. This may in part be related to the fact that most of the reports included in this review originate from Europe where prior to the introduction of routine childhood MenC immunisations, meningococcal serogroups B and C predominated [33]. Furthermore, a new hypervirulent clone of MenC with high CFR emerged in Europe and elsewhere during the 1990s causing several outbreaks as well as increased rates of endemic disease [34,35]. The absence of reported outbreaks due to MenB disease may reflect the hyperendemic rates caused by this serogroup, rather than focal outbreaks that have been associated globally with MenA, MenC and more recently MenW [34,36], but may also be related to exclusion of small MenB outbreaks from this review based on the definition of MG used. Most of the outbreaks outlined in this review were geographically limited, however one outbreak with eight cases of IMD occurring during the World Scout Jamboree in Japan 2015 spread internationally [8], and an outbreak during an international youth football tournament in 1997 (11 cases) crossed intra-European borders [28]. In contrast, previous outbreaks related to Haji have been significantly larger and resulted in massive intercontinental outbreaks of approximately 2000 and 2,400 individuals around the world in 1987 and 2000–01 respectively, including in Qatar, France and the UK [7,16,37–41].

Epidemiological data from non-outbreak settings during the pre-vaccination era demonstrate that the peak incidence of IMD occurs in infants, with a second, smaller peak occurring during adolescence and young adulthood [42–45]. The high rate of disease in infants is thought to be due to waning maternal antibody prior to the development of immunity during childhood [33,44]. The second peak in adolescents and young adults occurs in those individuals that fail to develop bacteraemic antibody and probably relates to social risk factors that places large groups of non-immune individuals in close settings such as universities and military bases [43,46]. Thus, it is unsurprising that the majority of cases of IMD reported during MGs occurred in 15–24 year-olds (around 80% of reported cases). Young children are less likely to be present during most typical MGs and thus are unlikely to be involved in such outbreaks. The exception is outbreaks occurring in refugee camps where all age groups may be involved and in one outbreak reported in a Rwandan refugee camp in Zaire, half of the patients were aged ≤10 years [26,27]. Similarly, both of the previously reported Hajj-related outbreaks of IMD involved a wide range of age groups including secondary cases in children after the return of pilgrims to their home countries [38–41].

In many MGs (e.g., sports events, university halls of residence, military bases) the demographic profile of attendees includes a high proportion of adolescents and young adults who have the highest rates of nasopharyngeal carriage of N. meningitidis and are the drivers for transmission of the organism within the population [47]. Furthermore, the social aspects of many MG’s (e.g., cruise ships, dance parties, sports events) are likely to encourage activities that are recognised risk factors for transmission of meningococci and development of IMD such as patronising bars and night clubs [22,46,48–51], active and passive smoking [46,48,50–54], and intimate kissing with multiple partners [14,46]. Among the studies included in this review, specific risk factors for IMD were only determined in one report of an outbreak of MenC disease in a university halls of residence in Illinois, USA, where patronising one particular campus bar increased the odds of IMD 17 times (95% confidence interval (CI) 2–410; p = 0.002) 1991 [21,22]. However, observations from other similar settings, such as living in college dormitories [55,56], highlight the roles of crowding and sharing common facilities in transmission of meningococci and increased risk of IMD that are relevant in the setting of MGs. In the UK, increased risk of IMD among university students compared with non-students of a similar age has been reported, with higher incidence among universities with a catered hall accommodation [57]. In addition, a high proportion of freshmen residents was found to be strongly associated with an increased incidence of IMD in university halls of residence [58]. In a cross-sectional study, the carriage rate of meningococci among freshmen at Nottingham University in the UK was shown to increase rapidly during the first week of term, from 7% on day 1 of term to 23% on day 4, demonstrating the role of social mixing, in increasing the rate of carriage of meningococci [51].

Military recruits share some common features with university students, particularly those residing in campus accommodation, with respect to age, living in semi-closed crowded settings, and engaging in high risk social activities. Over-crowding in some military training camps may increase the risk of outbreaks of IMD as reported in a military barracks in India when the accommodation capacity was exceeded by 34% [29]. However, similar outbreaks have been reported in two residential halls and one military barracks with fewer than 1000 occupants (ranging from 150 to 750) [59–61], which suggests that these settings pose risk factors that are not directly linked to the number of individuals involved, and that activities within these settings also play an important role in increasing the risk of IMD.

However, the occurrence of large intercontinental outbreaks of IMD associated with the Hajj pilgrimage despite the absence of many of these risk factors suggests that crowding is one of the most important risk factors for transmission of IMD among attendees of MGs. For example, bar patronage and drinking are non-existent during Hajj, intimate relationships even between spouses are avoided as an exercise of abstinence, and smoking is also discouraged. As such, crowding of individuals plays a pivotal role in the epidemiology of IMD during Hajj [7] and probably at other MGs. This is supported by studies in children in Denmark and New Zealand that have described a proportionate relationship between household density and the risk of IMD [62,63].

Acquisition of meningococci through the upper respiratory tract of a susceptible individual is considered the sentinel event prior to the development of IMD [64]. This can occur through coughing, sneezing and kissing. Despite a range of risk factors being identified for carriage of meningococci, the number and closeness of social contacts may be the most important [46]. Rates of carriage of meningococci have been shown to be increased in hyperendemic settings, particularly in closed and semi-closed populations, such as military recruits and university students, as well as during or shortly after outbreaks [65,66] compared to the background population rate. In a military camp in Norway, the meningococcal carriage rate reached up to 70% following the occurrence of a case of IMD [66]. Similarly, the carriage rate among residents of Makkah living near the Holy Mosque (the most densely populated area of the city) reached up to 86% just before the 1992 Hajj [67] following an outbreak among Umrah pilgrims during Ramadan (the fasting month) of 1992 that affected over 100 people. Conversely,
nasopharyngeal carriage of meningococci is an immunising event [68,69] and non-carriers are considered a high-risk group for IMD. In addition, variation in the incidence of disease caused by different serogroups and genotypes does not reflect the variation in their carriage rate. Therefore the relationship between carriage and development of IMD is complex and in most carriage studies limited strain characterisation has been performed to elucidate this relationship clearly. More detailed investigations using multilocus sequence typing (MLST) have demonstrated that despite extensive diversity of carriage strains of meningococci, a number of successful clones with global distribution exist, and hypervirulent clonal complexes are rare among strains from carriers [47]. Carriage studies have not been adequately conducted during outbreaks associated with non-Hajj/Umrah MGs; however during two MenC outbreaks in the 1990s in university settings in the USA and UK, meningococcal carriage rates of 25%-38% were demonstrated within the highest risk groups [21,22,25]. Carriage rates of the outbreak strains in these 2 outbreaks and a MenC outbreak in a Polish army unit in 2006 were between 0 and 10% with higher rates among the closest contacts [30]. These data suggest that the increased rates of carriage of any meningococci during outbreaks and in hyperendemic settings may simply be a marker of crowding and close social mixing which provide a favourable environment for rapid transmission of meningococci and increase the risk for the occurrence of IMD outbreaks.

Based on the small number of studies included in this review, and notwithstanding variability in seasons, settings, time and locations of the reported outbreaks, as well as inconsistent reporting, a crude estimate of incidence of IMD during MGs was calculated as 66 cases per 100,000 individuals over the duration of the MG. The incidence of IMD during non-outbreak settings in most industrialised countries ranges from 0.1–2/100,000 population per year [1,36] whereas rates of endemic disease in several countries of the African “meningitis belt” even between epidemics reaches up to 230 per 100,000 population per year [1]. The overall CFR calculated from the data available in these reports (14.9%) is similar to that reported previously (10–14%), with fatalities occurring across all age groups. Three outbreaks with ≥50% CFR occurred during short-lasting (e.g., one day) events. The CFR in these outbreaks may have been exaggerated by “statistical noise” due to the small number of identified cases. Alternatively, more prolonged outbreaks, may allow more time and opportunity to predict, prepare for, and manage cases, including timely referral to specialist centres, which may in turn decrease the CFR.

All common meningococcal serogroups, except serogroups X and Y (MenX and MenY), were isolated from outbreaks during MGs. MenA was the most common serogroup in terms of number of individual cases, whereas MenC was reported as the causative organism in a larger number of outbreaks. This reflects the global epidemiology of IMD which is affected by variations in geography and over time. The two largest outbreaks identified were caused by MenA during 1994–95 in Uganda and Zaire when MenA was the overwhelmingly predominant serogroup in Africa [70]. In contrast, the majority of outbreaks associated with MenC occurred in Europe during the emergence of a hypervirulent serogroup C, sequence type (ST) 11 clone in several European countries in the 1990s and 2000s [34,35]. The absence of serogroup X and Y disease in non-Hajj/Umrah MGs has been previously reported in a review by Gauthret et al. [71]. Hajj pilgrims have been found to carry a wide range of meningococcal serogroups including serogroup Y [72–74]. Despite this, the serogroups responsible for two major IMD outbreaks during Hajj have been MenA in 1987 and MenW in 2000–2001 [37]. Although MenX and MenY have not yet been reported to cause disease during a MG, both serogroups have increasingly been reported as a cause of IMD in various parts of the world including Europe [75,76].

Following sporadic cases of IMD standard preventive measures include chemoprophylaxis administered to close contacts [3]. During outbreaks and epidemics, chemoprophylaxis and/or immunisation may be extended to larger groups based on resources available, size of the outbreak and attack rate, as well as the size of the population(s) at risk [3]. Health education and behavioural change regarding hygiene, avoidance of intimate kissing, cessation of smoking and avoidance of smokers may be difficult to implement; however early treatment with antibiotics and supportive care is critical for improving outcome from IMD, and thus education on early recognition of signs and promoting health-care-seeking behaviour, especially during MGs, can be effective in identifying cases, controlling outbreaks and reducing morbidity and mortality. Furthermore, implementing social-distancing measures may be useful in specific situations [23,26,27,29,30]. Vaccines play an important role in preventing IMD outbreaks during MGs, demonstrated by a dramatic decline in rates of Hajj-related IMD cases reported in Saudi Arabia from 13.4 ± 9.3 cases/year in the pre-epidemic era (1995–1999) to 1.7 ± 2.3 cases/year in the post-epidemic era (2002–2011) (p = 0.02) following the introduction of compulsory MenACWY vaccination as part of visa requirements for Hajj pilgrims in 2002 [77]. In addition, the incidence of IMD reduced by nearly 94% from 1964 to 1998 in US military servicemen after incorporation of first bivalent (serogroups A and C), then quadrivalent (serogroups A, C, Wand Y) meningococcal (MenACWY) polysaccharide vaccines into routine immunisation of recruits since 1982 [78]. Similarly, meningococcal vaccines can be effective in helping to control outbreaks during MGs and to prevent secondary cases and outbreaks following dispersion of people after the event. For example, an outbreak of MenC disease in a town in West Yorkshire, UK, in 1995 that was linked to the local sports club, was controlled in part by offering immunisation and chemoprophylaxis to all children aged 2–18 years who were resident in the town or attended school there [79]. In addition, following introduction of compulsory meningococcal quadrivalent vaccine as a visa requirement for Hajj travellers in 2002, there were no cases of MenW disease in the UK in 2003 associated with the preceding Hajj, compared to the 25% increase in MenW cases that had been reported in the UK between 2000 and 2001, prior to the introduction of the new policy, largely among returning Hajj pilgrims and their contacts [80]. Of studies included in this review, mass immunisation was utilised during large outbreaks of MenA disease in two refugee camps in Africa, as well as two MenC outbreaks in university halls of residence in the USA and UK [21–23,25–27]. Mass chemoprophylaxis was provided to all exposed populations during outbreaks of MenC disease in a military barracks in Poland [30], a university halls of residence in the UK [25] and on a cruise ship [32]. The size of the population(s) at risk influences decisions regarding use of chemoprophylaxis (generally used for smaller gatherings) versus immunisation [3]. Furthermore, as highlighted in several reports, timely availability of vaccines impacts decisions on their use to control outbreaks [29,61].

In large scale MGs, such as international sports events, control of infectious diseases mainly depends on implementation of robust surveillance and reporting systems [81]. Nevertheless, in recent years, some experts have recommended meningococcal vaccines for travellers planning to attend MG events. For example, in 2008, attendees of the Beijing Olympic and Paralympic Games were advised to consider vaccination prior to travel [82]. Similarly, travellers to the FIFA World Cup in South Africa in 2010 were recommended to receive quadrivalent meningococcal vaccine [83,84]. To our knowledge, this is the first review that has assessed the burden of IMD in MGs other than Hajj/Umrah. The exclusion of articles published in languages other than English, the inability to capture data from outbreaks that have not been reported in
published literature, and the inconsistency of patient level data on all reported cases limits the ability to accurately determine incidence and case fatality rates. Furthermore, the overall quality of the evidence is modest. Nevertheless, findings from this review are consistent with recognised epidemiological and social risk factors for IMD and estimates of the burden of disease are consistent with reports of IMD from high incidence countries, with a similar overall CFR estimate to previously published reports. Specific risk factors for IMD during MGs could not be clearly identified within the limitations of this review. Based on the included studies, in contrast to outbreaks of IMD associated with Hajj/Umrah, outbreaks of IMD at other MGs tend to be smaller and affect mainly young people. However this may be a reflection of the fact that young people dominated the settings where the included outbreaks occurred rather than age per se being a risk factor. Most common meningococcal serogroups have been identified in such outbreaks with MenA and MenC being the most frequently isolated. High risk behaviours commonly adopted by youth, along with crowding, appear to be the main risk factors. Health education and vaccination should be considered as preventative measures for high risk non-Hajj/Umrah MGs, especially those involving youth. Inadequacy of available data on IMD during MGs other than Hajj and Umrah mandate the need for more studies to be conducted in this area, as well as the implementation of enhanced surveillance and reporting systems for IMD and other infectious diseases from a range of MGs.

5. Conflict of interest

Professor Robert Booy has received funding from Baxter, CSL, GSK, Merck, Novartis, Pfizer, Roche. Romark and Sanofi Pasteur for the conduct of sponsored research, travel to present at conferences or consultancy work; all funding received is directed to research accounts at The Children’s Hospital at Westmead. Dr Harunor Rashid received fees from Pfizer and Novartis for consulting or serving on an advisory board. The other authors have no competing interests to declare.

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References


1.3 Meningococcal carriage and disease during Hajj and Umrah


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Meningococcal Disease during Hajj, Umrah and other Mass Gatherings

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III. Abstract

Meningococcal disease is a systemic infection caused by a bacterium *Neisseria meningitidis*. There are an estimated 1.2 million worldwide cases of invasive meningococcal disease every year, resulting in up to 135,000 fatalities. Incidence of meningococcal disease fluctuates globally, with the highest annual incidence found in the African meningitis belt. High-risk behaviours such as active and passive smoking and intimate relationships (e.g. kissing), and semi-closed crowded settings (e.g. residence in university halls, military barracks and bar patronage) perpetuate transmission of the organism.

Mass gatherings can serve as epicentres for disease transmission. Hajj is the largest annual mass gathering that brings millions of Muslims pilgrims from around the world to amass in Makkah, Saudi Arabia. Intense congestion during Hajj, as well as shared accommodation and high-risk personal behaviours, magnify disease transmission including meningococcal disease. This pilgrimage is the most notable mass gathering and frequently magnifies meningococcal transmission and outbreaks. An outbreak in 1987 caused by serogroup A affected nearly 2000 individuals globally. A second outbreak caused by serogroup W occurred in 2000-2001, affecting more than 2400 individuals across the globe. Invasive meningococcal disease outbreaks in non-Hajj/Umrah Mass gatherings have been reported in university hall residents, military establishments, refugee camps, and sports and leisure events; these were mainly caused by serogroups A and C, and also led to an international spread. Mass immunization with multivariate vaccines and antibiotic chemoprophylaxis is a mainstay for invasive meningococcal disease prevention, successfully reducing morbidity and mortality. Without prevention, such mass
gatherings can influence global meningococcal epidemiology, likely by introducing invasive *N. meningitidis* strains to other regions.

**IV. Keywords:**

Meningococcal disease, Mass gathering, Hajj, outbreak, Arab world
V. Introduction

Meningococcal Disease

Meningococcal disease is a systemic infection caused by *Neisseria meningitidis*. The pathogen is a Gram-negative, aerobic bacterium of the *Neisseriaceae* family (Rouphael and Stephens 2012). There are 13 identified serogroups of *N. meningitidis*, with 6 serogroups (A, B, C, X, Y, and W) causing the majority of invasive meningococcal disease (IMD) (Rouphael and Stephens 2012). There are an estimated 1.2 million worldwide cases of IMD every year, resulting in up to 135,000 fatalities (Jafri et al. 2013); however, the incidence of meningococcal disease fluctuates globally, with annual incidence rates of 2 per 100,000 in most developed countries, and reaching up to 230 per 100,000 in the African meningitis belt (Figure 1): an endemic region in sub-Saharan Africa stretched from Senegal in the west of the continent to Ethiopia (Jafri et al. 2013). *N. meningitidis* is transmitted by direct contact with respiratory secretions, e.g., via sneezing. The pathogen usually colonises asymptotically in the nasopharyngeal cavity of carriers. It is estimated that up to 10% of the general population carry *N. meningitidis*, yet only 1% of carriers develop meningococcal disease (Rosenstein et al. 2001; Yazdankhah 2004). High-risk behaviours such as active and passive smoking (Cartwright et al. 1987; Stuart et al. 1988; Stanwell et al. 1994; Fischer et al. 1997; Neal et al. 2000; MacLennan et al. 2006; Rashid and Booy 2012) and intimate relationships (e.g. kissing) perpetuate transmission of the organism (Tully et al. 2006; MacLennan et al. 2006). The risk of transmission is further augmented through close contact in crowded settings e.g. residence in university halls, military barracks and bar patronage (Stuart et al. 1988; Stanwell et al. 1994; Edmond et al. 1995; Imrey et al. 1995, 1996; Cookson et al. 1998; Neal et al. 2000; Nelson et al. 2001; MacLennan et al. 2006).
Invasive infection with N. meningitidis can cause a number of clinical presentations. Septicemia and meningitis are considered the most common, with meningitis presenting in 80-85% of cases of IMD (Memish 2002). However, pneumonia (Racoosin et al. 1998), septic arthritis (Schaad 1980), conjunctivitis (Barquet et al. 1990), urethritis (Miller et al. 1979), and pericarditis (Rosenstein et al. 1999) can also occur rarely. Common symptoms of meningococcal meningitis and septicemia include onset of fever, nausea, vomiting and fatigue (Pace and Pollard 2012).

Early initiation of antibiotic therapy is the mainstay of clinical management of IMD (Cartwright et al. 1992). However, despite access to highly effective beta-lactam antibiotics, the case fatality of IMD has remained around 10% in treated cases (Thorburn et al. 2001). Furthermore, even with aggressive circulatory support in specialist centres, significant sequelae, including neurological damage, hearing loss and limb loss still occur in up to 20% of survivors (Healy et al. 2002). Thus, prevention remains the key goal in management of meningococcal disease. Antimicrobial chemoprophylaxis serves as the primary method for controlling outbreaks and direct contact transmission (CDC 2001; WHO 2008; Kushwaha et al. 2010; Yezli et al. 2016). During the 1960’s, high IMD rates within the United States of America (USA) military prompted the development of the meningococcal polysaccharide vaccine (Hankins et al. 1982). Vaccination is proven efficacious against IMD, providing immunological protection against major N. meningitidis serogroups for several years depending on the formulation. Quadrivalent (e.g. A, C, W and Y vaccine), bivalent (e.g. A/C and B/Y vaccines), and serogroup specific monovalent (e.g. meningococcal B vaccine), in conjugate and polysaccharide forms, as well as recombinant protein vaccines, are used globally in different settings (Vuocolo et al. 2018). With respect to meningococcal serogroups A, C, W and Y, more immunogenic polysaccharide-protein conjugate vaccines, compared to plain
polysaccharide vaccines are now used more widely, especially in developed nations, and these have been vital in controlling both endemic rates of IMD as well as outbreaks (Miller et al. 2001; Salleras et al. 2003; De Wals et al. 2004).

Global Epidemiology of Meningococcal Disease

The landscape of global burden of IMD varies, contingent on populations and settings, geographic area and climate, period, serogroup and clonal types. Epidemiology of IMD occurs either in epidemic, or endemic and hyperendemic rates (Harrison et al. 2009). Lack of data on meningococcal disease epidemiology from several countries hinders an accurate understanding of the magnitude of the worldwide burden of IMD; however, it is known that very high incidence rates occur in the African meningitis belt (Lapeyssonnie 1963). Most other countries in Africa, the Pacific and Western Europe have moderate incidence rates, while low incidence rates are predominantly found in Americas and Eastern Europe (Jafri et al. 2013).

Africa

Meningococcal disease has existed in the African region for more than 100 years. The highest global annual rates of IMD occur in the sub-Saharan countries of the African meningitis belt, with attack rates peaking up to 1000/100,000 population. Meningococcal meningitis is endemic in this region, and epidemics occur periodically during extremely hot and dry seasons. Crowded living conditions facilitate transmission and colonisation of the meningococci, and then the decreased air humidity during the dry season is likely to damage the pharyngeal mucosa enough to promote colonisation of the epithelium by the invading meningococci (Greenwood 1999). Serogroup A predominately causes IMD outbreaks in the region (Harrison et al. 2009), although smaller
outbreaks in the 1970’s were caused by serogroup C (Broome et al. 1983). Serogroup C outbreaks still continue to occur in this region, with the 2015 Niger outbreak being the most recent, understood to be the largest serogroup C outbreak in the meningitis belt (WHO 2015). In recent years sporadic cases of serogroup X IMD has affected up to 6700 individuals annually across Niger, Kenya, Togo, Burkina Faso, and Uganda (Xie et al. 2013). In African countries outside the meningitis belt, meningitis rates are relatively low at 0.14 cases per 100,000 population (Coulson et al. 2007). The incidence of the disease in the African meningitis belt is summarized in Table 1.

**Americas**

Early outbreaks recorded during the 20th century were believed to be caused by serogroup A (Rouphael and Stephens 2012). Incidence of IMD prior to World War II was high at 14/100,000 population, but decreased to 0.5-1.5/100,000 post war (Harrison et al. 2009); down to 0.12/100,000 in 2016 in the United States (Mbaeyi et al. 2018), and to 0.42/100,000 in post-vaccine period in Canada (Ali et al. 2014). The distribution of serogroups fluctuates over time. Studies suggest that serogroups B and C are common causes of IMD, however Y is emerging as a common etiological cause (Jackson and Wenger 1993; Imrey et al. 1996; Rosenstein et al. 1999). Recent serogroup distribution in the USA shows the predominance of serogroup Y followed by B, C and W (CDC 2008).

There are difficulties in describing the burden of IMD in the Latin American region due to limited published data. The overall incidence across the region is heterogenous ranging from 0.1/100,000 population in Mexico, up to 2/100,000 population in Brazil, where serogroups B and C are the
most common cause of disease. Recently, serogroups W and Y IMD are emerging in the region (Al-Tawfiq et al. 2010).

**Europe**

In the European region, *N. meningitidis* serogroup B and C are the most frequent causes of IMD. In 1999, hyperendemic rates of IMD at 1.67/100,000 population led to the introduction of meningococcal C conjugate vaccines in the United Kingdom (UK) followed by several the other countries, that reduced regional IMD to 1/100,000 in 2006. During the same time, case fatalities ranged between 6% and 8%, however, vaccination programs have decreased both the incidence of disease and associated fatalities (Chandra and Ramsay 2007).

**Western Pacific**

Data to describe the epidemiological scope of meningococcal disease in Western Pacific region is limited. Epidemics in the past century across China, Hong Kong, Mongolia, Taiwan and the Philippines was predominantly caused by serogroup A (Vyse et al. 2011), with rates of up to 500/100000 in China (Zhang et al. 2008). Serogroup B and C also occurred with incidence rates of 20/100,000 in South Vietnam (Oberti et al. 1981). Recent rates of IMD are relatively low across China, Philippines, South Korea, Singapore, Taiwan (Jafri et al. 2013), and Japan (Fukusumi et al. 2016). Serogroup A outbreaks have occurred in India more recently (Nair et al. 2009), with serogroups C, W, and Y emergent in China (Ni et al. 2008), Singapore (Wilder-Smith et al. 2002), and Taiwan (Chiou et al. 2006) respectively.

Australia is predominantly burdened by *N. meningitidis* serogroups B and C (Rouphael and Stephens 2012). IMD incidence was high in the 1990’s at a rate of 3/100,000 (Jelfs and Munro
2001); however, declined to 1.3/100,000 in 2006 due to serogroup C conjugate vaccinations. Case fatality rates remain stagnant at 7% (Tapsall 2008). New Zealand is characterised as a highly endemic country with disease predominantly caused by serogroup B (O’Hallahan et al. 2005) with incidence rates up to 17.4/100,000 in 2001; subsequently declining to 2.6/100,000 in 2007, in part due to the use of outer membrane vesicle (OMV) meningococcal serogroup B immunisation (Baker et al. 2001; O’Hallahan et al. 2005).

**Eastern Mediterranean Region**

Accurate information regarding the epidemiology of meningococcal disease in the Eastern Mediterranean region is hindered due to limited data and fluctuations in disease burden across the region. Meningococcal disease in Saudi Arabia is mainly caused by serogroups A and W, although cases with serogroups B and C persist (Ceyhan et al. 2012). Disease rates in Saudi Arabia are high during epidemic periods, mainly influenced by Hajj pilgrimage to Makkah, reaching up to 12.83/100,000. During non-epidemic periods IMD rates remain low with rates only peaking to 1.65/100,000 (Jafri et al. 2013). Gulf states such as Bahrain, Kuwait, United Arab Emirates, and Qatar have relatively low IMD rates occurring at below 2 cases per 100,000 population (Ceyhan et al. 2012).
VI. Mass gatherings

Mass gatherings (MGs) are defined as either an organised or unplanned gathering of people for a common purpose at a specific place and time. The number of people gathering can be as low as a 1000 people, but can reach up to millions, wherein the influx of participants can stress the host community’s health planning and response resources (WHO 2008). The location, attendance and duration of the gathering is contingent on the type of event. The event may be a one-time gathering (e.g. state funeral), or of a more frequent pattern (e.g. annual Hajj). It can last from several hours (e.g. sports events) up to several months (e.g. The Kumbh Mela pilgrimage and festival in Hinduism lasts ~2.5 months and attracted 60 million people in 2001). Different MG conditions coincide with variable health monitoring and control efforts during the event, ranging from an absence of health monitoring to highly complicated health management and surveillance arrangements. MGs with intense congestion, shared accommodation and high risk personal behaviours magnify communicable disease transmission such as IMD, and become settings for meningococcal outbreaks (e.g. 2004 EURO football tournament) (Gonçalves et al. 2005; Tully et al. 2006; Wilder-Smith 2007; Memish et al. 2012). As such, the long periods spent at Hajj pilgrim sites, in addition to the extreme heat, crowded accommodation, traffic jams, and the generally advanced age of pilgrims, amplifies the rate of N. meningitidis transmission (Ahmed et al. 2006; Al-Tawfiq and Memish 2014).

Hajj and Umrah

The Hajj is a religious Muslim event that annually gathers millions of pilgrims from around the world in Makkah, Saudi Arabia. The gathering is a week-long pilgrimage, taking place on specific
days during the 12th month of the Islamic lunar calendar. Every able-bodied Muslim must undergo the pilgrimage at least once in his/her lifetime to enact the journey and rituals performed by the Prophet Mohammed (PBUH). Pilgrims continue to visit Makkah throughout the year, embarking on a smaller ritual called the Umrah. International travel renders a high influx of participants performing the Umrah, especially during the three months preceding the Hajj (Ahmed et al. 2006).

Hajj pilgrimage is the most notable mass gathering that magnifies meningococcal transmission and outbreaks. An outbreak in 1987 caused by serogroup A affected nearly 2000 individuals internationally. Its subsequent introduction to the African meningitis belt caused major waves of serogroup A epidemics with rates of up to 1000 cases per 100,000 (al-Gahtani et al. 1995; Yezli et al. 2016). A second international outbreak caused by serogroup W occurred in 2000-2001, affecting more than 2400 individuals across Europe, America and the Middle East (Ahmed et al. 2006).

**Meningococcal Disease at Hajj**

*Pre-outbreak era*

Prior to the 1980’s, health surveillance was limited to describing the nature of IMD during Hajj due to a lack of accurate and more specific data. It is likely that meningococcal disease during Hajj was uncommon. Although outbreaks did occur, these were not routinely documented (al-Gahtani et al. 1995). Since the 1980’s, IMD has become a significant public health burden based on the historic persistence among Hajj pilgrims (Yezli et al. 2016).
First outbreak at Hajj in 1987

The significance of the Hajj in influencing local and global IMD epidemiology was established from multiple outbreaks occurring in Makkah. In 1987, the first reported Hajj-related international outbreak affected 1841 people, with the majority of cases coming from Makkah, Medina, and Jeddah (al-Gahtani et al. 1995). *N. meningitidis* serogroup A clonal complex III-1 was the etiological cause, believed to have been introduced into Makkah by Hajjis (pilgrims) from South Asia (Moore et al. 1989); this corresponded with serogroup A outbreaks in India and Nepal (Cochi et al. 1987) preceding the Hajj as described in Figure 1. South Asian Hajjis comprised 10% of the pilgrim population that year, and had the highest attack rates compared to pilgrims from other nationalities (Moore et al. 1989). The disease later spread to local populations and international pilgrims (Ahmed et al. 2006). That year, IMD rates in Saudi Arabia increased to 12.83 cases per 100,000 (Ceyhan et al. 2012). Returning pilgrims became carriers and transmitted *N. meningitidis* in their respective countries, initially through direct contacts (Memish 2002), causing further outbreaks. The first one of these was detected in neighbouring Qatar, with 112 reported serogroup A cases that same year (Ceyhan et al. 2012). Subsequent introduction of serogroup A III-1 into the African Meningitis belt by returning pilgrims aggravated the regional disease epidemiology. Although *N. meningitidis* serogroup A existed in the region since 1915 (Olyhoek et al. 1987), the clonal type III-1 was only identified after the 1987 Hajj (Moore et al. 1989). Outbreaks later occurred in 1988 in Sudan and Chad, affecting 7500 and 18,000 people respectively (Moore et al. 1989). No associated outbreaks occurred despite the introduction of *N. meningitidis* to Egypt, possibly due to a lack of required environmental and social factors to instigate an epidemic (Moore et al. 1989).
Spread of disease to Europe also occurred. Thirty-four cases of serogroup A disease were recorded in the UK, the majority of which were in children (Jones and Sutcliffe 1990). Four direct contacts of returning pilgrims were reported to have serogroup A IMD in the city of Amiens in France, where three cases were in people under the age of 18, and one in an adult (Denamur et al. 1987). In the USA, 9 cases of IMD were reported and 7% of returning pilgrims carried serogroup A meningococci in their throat (36/550 of inbound passengers) (Moore et al. 1988).

In response to the impeding health threat, the Saudi Arabian authorities mandated bivalent A/C polysaccharide vaccination for visiting pilgrims and local residents and compulsory oral ciprofloxacin for visitors from sub-Saharan Africa (Ahmed et al. 2006; Memish et al. 2013); these measures controlled IMD in Saudi Arabia at the time (al-Gahtani et al. 1995).

**Second Outbreak at Hajj in 2000 and 2001**

The mandatory bivalent A/C vaccine policy was very effective for more than a decade until the year 2001 when a new wave of IMD outbreaks occurred during the Hajj seasons of 2000 and 2001, affecting at least 2,400 people globally (Ahmed et al. 2006). Nearly 50% of cases were caused by a newly emerging serogroup W, a strain with no previous record of causing major epidemics. Serogroup W was first identified in the 1970s and had been associated with a small Saudi Arabian outbreak in 1996. This was the same strain that caused disease in Mali, Algeria, and Gambia in the 1990’s (Mayer et al. 2002).

A total of 1.7 million Muslims assembled at the Hajj of 2000 (Lingappa et al. 2003). Increased meningococcal rates were observed in Saudi Arabia during Hajj that year, with 49% and 31% of cases coming from Makkah and Medina respectively (Memish et al. 2013). A total of 253 cases...
(out of 264) were caused by serogroup W, making it the largest known outbreak caused by this serogroup. Overall, 78 fatalities were recorded, resulting in a case fatality rate of 28% (Lingappa et al. 2003). Higher case fatalities (46%) were observed among international pilgrims compared to Saudi Arabian residents (12%). Among patients admitted to hospital, fatalities peaked as high as 60% (Lingappa et al. 2003). Moreover, pilgrims who had received bivalent serogroup A/C vaccines had higher frequencies of serogroup W IMD (Lingappa et al. 2003). By August that year, more than 400 cases of serogroup W disease were reported across Belgium, UK, France, USA, Kuwait, Morocco, Oman, Indonesia, Singapore, Finland, Denmark, Sweden, Norway, Germany, Netherlands, and Saudi Arabia. All cases were returning pilgrims and close contacts (Handysides et al. 2000; Lingappa et al. 2003; Ceyhan et al. 2012). Among American pilgrims administered quadrivalent serogroup A/C/Y/W vaccines, only 2 cases were recorded from a return Hajji and a direct contact (Fine et al. 2000).

In 2001, smaller associated outbreaks occurred globally, resulting in 109 cases and 35 deaths (WHO 2001), with a majority (~50%) of cases caused by serogroup W (Memish et al. 2003). Intercontinental spread analogous with the 1987 and 2000 Hajj epidemics was apparent, as serogroup W carriage increased among returning pilgrims from the USA and Singapore (Wilder-Smith et al. 2002; Dull et al. 2005). The economic, social and health burden of the 2000-2001 epidemics led to policy revisions leading to replacing the mandatory bivalent serogroup A/C vaccination with quadrivalent serogroup A, C, Y and W polysaccharide vaccine. Quadrivalent meningococcal vaccination was made compulsory for all residents over 5 years of age living near the Hajj sites, and to all healthcare/government workers serving at the Hajj (Memish et al. 2013).

*Meningococcal disease at Umrah*
Following the 1987 outbreak, mandatory bivalent serogroup A/C vaccines and oral ciprofloxacin treatment were administered to local residents and international pilgrims to control meningococcal disease (Al-Ghamdi and Kabbash 2011). Vaccination policies eventually restrained outbreaks. However, small Umrah related serogroup A and W outbreaks occurred in Makkah and Jeddah in the 1990’s, coinciding with the Ramadan month (al-Gahtani et al. 1995; El Bushra et al. 2000). In 1992, an outbreak in Makkah resulted in 102 serologically confirmed cases and 80 suspected cases. Fifty-nine percent of confirmed cases, and 24 percent of suspected cases, were religious visitors. Case fatality rates were as high as 14.7% for confirmed cases (al-Gahtani et al. 1995). A similar outbreak occurred in Jeddah that same year, resulting in 41 serologically confirmed cases, of which 32% were religious visitors, and case fatality rates reached 19.5% (Bushra et al. 1995). Intercontinental spread was observed with consequent serogroup A outbreaks occurring in Zambia from 1992 to 1994 (Luo et al. 1998). Increased meningococcal disease rates in Makkah during the 1997 Umrah resulted in an outbreak with 72 cases; 51 were bacteriologically confirmed as being predominantly related to serogroup A clonal complex III-1. The cases were predominantly Umrah visitors (70.6%) and non-Saudi residents (25.5%), with a mean age of ~48 years. Case fatality among patients reached 27.5% and did not differ among residents and Umrah visitors (Al Salman and El Bushra 1998).

**Current Situation at Hajj**

The use of quadrivalent (A, C, W and Y) vaccine uptake has drastically decreased meningococcal epidemics. No outbreaks have occurred since the mandatory quadrivalent vaccine policy was introduced, with only 184 laboratory-confirmed cases of IMD reported in Saudi Arabia from 2002 to 2011, and disease rates similar between Hajj and non-Hajj months. Among confirmed cases in
Saudi Arabia, only 9% are Hajj/Umrah pilgrims (Memish et al. 2013). During the period between 1995 and 2011, citizens and residents in the main Hajj pilgrimage destinations had a high cumulative incidence (Makkah: 9 cases/100,000, Medina: 4.5 cases/100,000) (Memish et al. 2013) (Figure 2). Serogroups A and W still cause most cases of IMD; however, sporadic cases from serogroups B, C, X, Y, and Z still occur (Memish et al. 2013). Mean annual rates of IMD also declined to two cases per 100,000 during epidemic periods. Recent case fatality rates remain low at 11.4% during epidemic periods, with higher rates among pilgrim visitors (28.9%) compared to Saudi residents (10.4%) (Memish et al. 2013). However, Hajj attendance is still associated with increased meningococcal carriage, which raises concerns on the effectiveness of the vaccine in reducing carriage (Table 2).

The Saudi Arabian Ministry of Health has legislated that anyone arriving at Hajj zones for Umrah, Hajj or for seasonal work, is required to provide a valid certificate of vaccination with a quadrivalent serogroup A, C, Y and W meningococcal vaccine administered no less than 10 days prior to arrival. Local pilgrims are also required to submit such a certificate in order to obtain their Hajj permit (Al-Tawfiq et al. 2017). Moreover, the use quadrivalent conjugate vaccines are recommended over polysaccharide equivalents where available and affordable (Ceyhan et al. 2013). The Saudi Arabian authority may opt to administer prophylactic antibiotics to some travellers (e.g. those from African meningitis belt with dubious vaccination record) at the points of entry if deemed necessary (Algarni et al. 2016). The Kingdom of Saudi Arabia has also improved its capacity to accommodate for unpredictable health threats to pilgrims. Modern facilities (e.g. hospitals, healthcare centres), and medical specialists are made available to provide healthcare to all Hajj and Umrah pilgrims free of charge to avert outbreaks and fatalities (Memish
With Saudi Arabian initiative to increase Hajj and Umrah participation as an integral part of its 2030 vision, further expansion of the region’s preventative measures and health emergency preparedness and response systems is urgently needed to ensure optimum health and safety of all pilgrims.

In summary, intense crowding, shared accommodation and compromised hygiene in mass gatherings such as the Hajj amplify IMD transmission. Intercontinental outbreaks of serogroup A N. meningitidis in 1987, and serogroup W in 2000-2001 affected thousands of pilgrims and their direct contacts. Mandatory bivalent serogroup A/C vaccine implementation following the 1987 outbreak was ineffective at preventing the 2000-2001 outbreaks, which were, however, subsequently controlled through the use of quadrivalent (A, C, Y and W) vaccines.

**Meningococcal Disease at Non-Hajj/Umrah Mass Gathering**

IMD outbreaks in non-Hajj/Umrah MGs have been reported in closed and semi-closed populations such as university hall residents, military establishment recruits, refugee camps residents, and participants of sports and leisure events (Badahdah et al. 2018) (Table 3). All common serogroups except for X and Y have been associated with outbreaks in these settings, with serogroup A and C being the most frequently reported. The populations most affected are adolescents and young adults aged 15-24 years, who have the highest rates of N. meningitidis carriage as sources of disease transmission (Caugant et al. 2007). However, outbreaks in African refugee camps affected all age groups, including children aged ≤ 10 years (Haelterman et al. 1996; Heyman et al. 1998; Santaniello-Newton and Hunter 2000). Military recruits and university freshmen are categorised as high-risk groups (Nguyen-Van-Tam et al. 1999; Nelson et al. 2001; Grecki and Bienias 2006;
Kushwaha et al. 2010) as they share some common features with respect to age, live in semi-closed environments, and engage in high risk social activities including patronising bars and clubs (Stuart et al. 1988; Edmond et al. 1995; Imrey et al. 1996; Cookson et al. 1998; Neal et al. 2000; MacLennan et al. 2006), are active and passive smokers (Stuart et al. 1988; Stanwell et al. 1994; Fischer et al. 1997; Cookson et al. 1998; Neal et al. 2000; MacLennan et al. 2006) and engage in intimate kissing (Tully et al. 2006; MacLennan et al. 2006). These established high-risk behaviours are correlated with other MGs, including sports and leisure events, including a European football tournament (Reintjes et al. 2002; Gonçalves et al. 2005), rugby matches (Orr et al. 2001), cruise ships (Stefanelli et al. 2012), World Scout Jamboree (ECDC 2015), and dance parties in Brazil (Gorla et al. 2012) and USA (Finn et al. 2001). Intense congestion and shared accommodation along with compromised hygiene are also pivotal in IMD serogroup A, for example the outbreaks occurring in refugee camps in Uganda (Santaniello-Newton and Hunter 2000) and Zaire in 1994 (Heyman et al. 1998).

Mass immunisation was implemented in serogroup A and C outbreaks in African refugee camps (Haelterman et al. 1996; Heyman et al. 1998; Santaniello-Newton and Hunter 2000), and university accommodations in the USA and UK (Imrey et al. 1995, 1996; Gilmore et al. 1999). Chemoprophylaxis treatment was administered to exposed groups during serogroup C outbreaks in university residence halls (Gilmore et al. 1999), military barracks (Grecki and Bienias 2006) and on a cruise ship (Stefanelli et al. 2012) to control the spread of disease.

**Comparing and Contrasting Hajj vs. Non-Hajj Outbreaks**

Both Hajj and non-Hajj outbreaks of IMD share common characteristics, particularly the closed and semi-closed settings, along with congestion and shared accommodations; however, several
distinctions can be made between them. Common serogroups have been isolated from outbreaks in both MG settings, although serogroups A and C strains are the most frequent etiological causes in non-Hajj MGs outbreaks compared to serogroups A and W strains in Hajj-associated epidemics. In comparison to non-Hajj MGs, outbreaks of IMD at Hajj tend to be large and involve older people. This may be explained by the fact that younger people frequent non-Hajj MGs more commonly than at the Hajj where attendants are predominantly older adults. The high-risk behaviours demonstrated by the youth at these settings increase the risk of transmission of meningococci and of IMD. However, it is important to recognise the magnitude of health burden from Hajj-associated epidemics compared to the relatively smaller outbreaks occurring at other MG. Large local and intercontinental epidemics occurred during and following the Hajj even despite the absence of classical risk behaviours (smoking is discouraged during Hajj, bar patronage and drinking are also non-existent, and intimate relations even between spouses are avoided as an exercise of abstinence), suggesting that crowding itself is an important risk factor for transmission of IMD among attendees of any MG.

**VII. Conclusion**

Meningococcal disease remains a global public health threat, causing worldwide morbidity and mortality. The complexity of meningococcal epidemiology and lack of data from certain areas makes it difficult to fully describe the worldwide burden of disease. Mass gatherings such as the Hajj and Umrah serve as epicentres of disease transmission and intercontinental spread. Importation of Muslim pilgrims from all corners of the world to Makkah has drastically affected meningococcal disease epidemiology in Saudi Arabia. Without prevention, such mass gatherings can influence global meningococcal epidemiology, introducing invasive *N. meningitidis* strains to
other regions. Intercontinental outbreaks arising from Makkah have been documented in 1987 and 2000-2001, predominantly caused by serogroups A and W respectively. On the other hand, local Hajj and Umrah related outbreaks coinciding with these international outbreaks were caused by serogroup A.

Subsequent bivalent serogroup A/C vaccines administered to pilgrims after 1987 reduced the burden of disease in succeeding years, yet failed to provide pilgrims immunity to serogroup W disease, which caused waves of local and global outbreaks in 2000 and 2001. As a result, quadrivalent serogroup A, C, W and Y vaccination became the first line of defence for pilgrims against IMD, and is still used to control local and international Hajj-related outbreaks.

Currently, the Saudi Arabian authorities require quadrivalent serogroup A, C, W and Y vaccinations for all local and international pilgrims, as fulfilment for Hajj permits and visa approvals. Antibiotic chemoprophylaxis is also administered to international visitors coming from the highly endemic African meningitis belt. Strict adherence to this policy at all entry points to Saudi Arabia and Makkah in particular, along with continuing healthcare expansion are observed in anticipation of the threat of IMD outbreaks during the Hajj and Umrah.

IMD outbreaks have also been reported in other MGs and crowded settings such as sporting events, university residences and refugee camps wherein some social behaviours (e.g. smoking, intimate relationships and bar patronage) along with crowdedness have contributed to these smaller outbreaks, mainly caused by serogroups A and C. Similar to control efforts at the Hajj and Umrah, vaccinations and antibiotic treatments were critical in controlling these outbreaks.
VIII. References


Cartwright KA V, Stuart JM, Jones DM, Noah ND (1987) The Stonehouse survey:


Neisseria meningitidis strain. Lancet 2:260–3


diseases 2:880–8


IX. Figures and Tables

Figure 1. The first Hajj-related international outbreak in 1987 started at Nepal, reached Makkah and spread to other parts of the world.
Figure 2. Number of confirmed cases of meningococcal diseases in Saudi Arabia and Makkah from 1987 to 2015*

* Cases from Makkah were not available for year 1987, and cases from Saudi Arabia were not available from year 1989-1994
<table>
<thead>
<tr>
<th>Period</th>
<th>Attack rate(^a) (per 100,000)</th>
<th>Year</th>
<th>Country/Region</th>
<th>Dominant Serogroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>1971-1980</td>
<td>360</td>
<td>1977</td>
<td>Nigeria, Zaria</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>517</td>
<td>1979</td>
<td>Burkina Faso</td>
<td>C</td>
</tr>
<tr>
<td>1981-1990</td>
<td>593</td>
<td>1986</td>
<td>Niger</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>267</td>
<td>1990</td>
<td>Kenya</td>
<td>A</td>
</tr>
<tr>
<td>1991-2000</td>
<td>608</td>
<td>1992</td>
<td>Burundi</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>300</td>
<td>1993</td>
<td>Cameroon</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>465</td>
<td>1995</td>
<td>Niger</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>1605</td>
<td>1996</td>
<td>Burundi</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>984</td>
<td>1997</td>
<td>Gambia</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>550</td>
<td>1997</td>
<td>Ghana</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>652</td>
<td>1997</td>
<td>Togo</td>
<td>NA</td>
</tr>
<tr>
<td>2001-2010</td>
<td>10(^b)</td>
<td>2004</td>
<td>AMB(^c)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>6(^b)</td>
<td>2005</td>
<td>AMB(^c)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>13.5(^b)</td>
<td>2006</td>
<td>AMB(^c)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>14.5(^b)</td>
<td>2007</td>
<td>AMB(^c)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>10(^b)</td>
<td>2008</td>
<td>AMB(^c)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>22(^b)</td>
<td>2009</td>
<td>AMB(^c)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>728</td>
<td>2009</td>
<td>Nigeria</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>8(^b)</td>
<td>2010</td>
<td>AMB(^c)</td>
<td>A</td>
</tr>
<tr>
<td>2011-2019</td>
<td>6(^b)</td>
<td>2011</td>
<td>AMB(^c)</td>
<td>W</td>
</tr>
<tr>
<td></td>
<td>7(^b)</td>
<td>2012</td>
<td>AMB(^c)</td>
<td>W</td>
</tr>
<tr>
<td></td>
<td>4.5(^b)</td>
<td>2013</td>
<td>AMB(^c)</td>
<td>W</td>
</tr>
<tr>
<td></td>
<td>1037</td>
<td>2015</td>
<td>Aliero, Nigeria</td>
<td>NA</td>
</tr>
</tbody>
</table>

AMB, African meningitis belt; NA, no data available.
\(^a\)Includes confirmed and suspected cases
\(^b\)Rounded to the nearest half.
\(^c\)Overall incidence rate of confirmed and suspected meningococcal meningitis in the African meningitis belt for the respected year.
<table>
<thead>
<tr>
<th>Year</th>
<th>Season</th>
<th>Study population</th>
<th>Study design</th>
<th>Carriage rate</th>
<th>Main serogroup</th>
<th>Remarks</th>
<th>Reference</th>
</tr>
</thead>
</table>
| 2001 | Hajj   | Makkah and Jeddah residents | Prospective Study | Pre-Hajj: 7.2%  
Post-Hajj: 0.8%  
Overall: 4.7% | MenW | 4.6% of pilgrims were administered antibiotics | (Balkhy et al. 2003) |
| 2001 | Hajj   | US pilgrims travelling to and from JFK Airport, NY | Prospective Study | Pre-Hajj: 0.8%  
Post-Hajj: 2.6% | Non-serogroupable | 49% of pilgrims were administered antibiotics | (CDC 2001) |
| 2001 | Umrah | Thai Pilgrims | Cross-sectional | Post Hajj: 0% | Not Applicable | | (Phrom-in 2002) |
| 2001 | Umrah | Singaporean pilgrims | Cross-sectional | Post Umrah: 1.30% | Non-serogroupable | 7% of pilgrims were administered antibiotics | (Wilder-Smith et al. 2003) |
| 2001 | Hajj   | Singaporean Pilgrims | Prospective Study | Pre-Hajj: 0.5%  
Post-Hajj: 17% | MenW | 8.2% of household contacts acquired carriage | (Wilder-Smith et al. 2002) |
| 2002 | Hajj   | British Pilgrims | Prospective Study | Pre-Hajj: 8.3%  
Post-Hajj: 6.3% | Non-serogroupable followed by MenB | 21% of pilgrims were administered antibiotics | (El Bashir et al. 2004) |
| 2003 | Hajj   | Iranian Pilgrims | Prospective Study | Pre-Hajj: Group 1: 5.2%, group 2: 8.1%  
Post-Hajj: Group 1 4.6%, Group 2: 0% | Non-serogroupable | Single dose of 500g oral ciprofloxacin reduced risk of carriage | (Alborzi et al. 2008) |
| 2010 | Hajj   | Turkish Pilgrims | Prospective Study | Pre-Hajj: 13%  
Post-Hajj: 27% | MenW | 28.2% of household contacts acquired carriage | (Ceyhan et al. 2013) |
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Location</th>
<th>Study Type</th>
<th>Pre-Hajj:</th>
<th>Post-Hajj:</th>
<th>Vaccine Type</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>Hajj</td>
<td>Iranian Pilgrims</td>
<td>Prospective Study</td>
<td>0%</td>
<td>1.4%</td>
<td>Not described</td>
<td>58.5% of pilgrims received quadrivalent meningococcal A, C, W and Y vaccine (Metanat et al. 2015)</td>
</tr>
<tr>
<td>2014</td>
<td>Hajj</td>
<td>International Pilgrims arriving at Saudi Arabia</td>
<td>Paired-Cohort</td>
<td>2.5%</td>
<td>0.15%</td>
<td>Non-serogroupable and MenB</td>
<td>All pilgrims received quadrivalent meningococcal A, C, W and Y vaccine (Memish et al. 2017)</td>
</tr>
<tr>
<td>2014</td>
<td>Hajj</td>
<td>Australian Pilgrims</td>
<td>Cross sectional</td>
<td>0.06%</td>
<td>0.02%</td>
<td>MenW</td>
<td>78.7% of pilgrims received quadrivalent meningococcal A, C, W and Y vaccine (Azeem et al. 2017)</td>
</tr>
</tbody>
</table>

US – United States of America, MenB – *Neisseria meningitidis* serogroup B, MenW – *N. meningitidis* serogroup W
<table>
<thead>
<tr>
<th>Serogroup</th>
<th>Year</th>
<th>Place of MG</th>
<th>Setting</th>
<th>Age of affected individuals</th>
<th>Reported outbreaks</th>
<th>Cases</th>
<th>Fatalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>MenA</td>
<td>1994, 2006</td>
<td>Uganda, Zaire, India</td>
<td>Refugee Camps, Military Barracks</td>
<td>All</td>
<td>3</td>
<td>388</td>
<td>51</td>
</tr>
<tr>
<td>MenB</td>
<td>2007</td>
<td>Spain</td>
<td>Sporting event</td>
<td>16 years</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>MenC</td>
<td>1991, 1997,</td>
<td>USA, United Kingdom, Belgium, Brazil,</td>
<td>University Campus Residence, Military Barracks,</td>
<td>12-59 years</td>
<td>7</td>
<td>47</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>2001, 2006,</td>
<td>Italy, Poland</td>
<td>Sports Events, Military Barracks, Dance Party,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2009, 2012</td>
<td></td>
<td>Cruise Ship</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MenW</td>
<td>2015</td>
<td>Japan</td>
<td>World Scout Jamboree</td>
<td>ND</td>
<td>1</td>
<td>8</td>
<td>ND</td>
</tr>
</tbody>
</table>

Legend:

**Figure 1**: Should be placed immediately **before** the heading “Second Outbreak at Hajj in 2000 and 2001”.

**Figure 2**: Should be placed between paragraph 1 and 2 of the heading “Current Situation at Hajj”. The label “*Cases from Makkah was not available for year 1987 and cases from Saudi Arabia was not available from year 1989-1994*” should be inserted underneath the figure.

**Table 1**: Should be placed immediately after subheading “Africa” of heading “Global Epidemiology of Meningococcal Disease”.

**Table 2**: Should be placed between paragraph 1 and 2 of the heading “Current Situation at Hajj”

**Table 3**: Should be placed between paragraph 1 and 2 of the heading “Meningococcal Disease at Non-Hajj/Umrah Mass Gathering”
Chapter 2: Immunogenicity, Immune Persistence and Induction of Immune Memory by Meningococcal Serogroup C Conjugate Vaccines


What is the context?

- Meningococcal conjugate vaccines are highly immunogenic.
- Different carrier proteins are used in marketed conjugate vaccine such as TT, DT and CRM₁₉₇.
- Gradual waning of antibody responses is observed following administration of all conjugate vaccines.

What is new?

- A systematic review of trials on various brands of MenC vaccines conjugated to different carrier proteins to compare their immunological profile.

What is the impact?

- The immunological profile appears to be varied between vaccine brands.
- The tetanus toxoid conjugated formulation had shown a distinctly superior immune profile compared to meningococcal vaccines conjugated to other carrier proteins.
Update on the use of meningococcal serogroup C CRM$_{197}$-conjugate vaccine (Meningitec) against meningitis

Al-Mamoon Badahdah, Harunor Rashid & Ameneh Khatami

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Update on the use of meningococcal serogroup C CRM$_{197}$-conjugate vaccine (Meningitec) against meningitis

Meningitec is a CRM$_{197}$-conjugated meningococcal serogroup C (MenC) vaccine, first licensed in 1999. It has been used as a primary and booster vaccine in infants, toddlers, older children and adults, and has been shown to be immunogenic and well-tolerated in all age groups, including premature infants. Vaccine effectiveness has been demonstrated using combined data on all three licensed MenC conjugate vaccines. Evidence from clinical trials, however, suggests that the different MenC conjugate vaccines behave differently with respect to the induction and persistence of bactericidal antibody and generation of immune memory. It appears that Meningitec has a less favorable immunologic profile compared particularly to tetanus toxoid (TT) MenC conjugate vaccines. Data from comparative trials have raised interesting questions on priming of the immune system by conjugate vaccines, particularly in infants. The results from these and other studies are reviewed here with specific focus on Meningitec.

Keywords: Neisseria meningitidis ● meningococcal serogroup C ● conjugate vaccine ● meningitis ● Meningitec

Neisseria meningitidis is a pathogen restricted to humans and causes endemic and epidemic meningococcal disease globally. Based on the biochemical composition of the capsule, meningococci have been classified into 13 serogroups; five of these (serogroups A, B, C, Y and W$_{135}$) account for approximately 90% of infections worldwide.[1] Serogroup C is highly associated with invasive disease.[2]

Meningococcal serogroup C (MenC) polysaccharide vaccines have been used since the 1970s for individuals at high risk of invasive disease, such as military recruits.[3] Although polysaccharide vaccines have been effective in preventing disease in older children and adults, they are poorly immunogenic in infants, are not protective in children under 2 years of age and have no significant impact on nasopharyngeal carriage of meningococci.[4,5] To overcome these limitations, protein conjugate vaccines were developed by binding the MenC capsular polysaccharide to a carrier protein such as mutant diphtheria toxin (CRM$_{197}$) or tetanus toxoid (TT). These protein–polysaccharide conjugate vaccines are thus able to induce immune responses through T-cell-dependent pathways, making them immunogenic even in young infants. In addition, conjugate vaccines are able to induce immune memory, as demonstrated by an anamnestic response to booster vaccines or polysaccharide challenge, [6] and have also been shown to reduce nasopharyngeal carriage of meningococci,[7] leading to the development of ‘herd immunity’ through reduced transmission of organisms within a population.

The increase in incidence of invasive MenC disease due to the ST-11 strain in several European countries in the late 1990s led to the licensure of MenC conjugate vaccines first in the United Kingdom (UK) in 1999, and later in several other countries, based on safety and immunogenicity data.[8] The introduction of MenC conjugate vaccines through routine
childhood immunization programs and catch-up campaigns was shown to effectively prevent invasive disease, reduce nasopharyngeal carriage in vaccinated populations and also led to a substantial decline in rates of disease in unvaccinated individuals.[7,9,10] This has resulted in ‘near elimination’ of MenC meningitis in many countries.[11] The incidence of MenC disease in England and Wales, for example, fell from 1.85 per 100,000 population before the introduction of the vaccines to 0.02/100,000, a decade after their introduction.[12] Similarly, in the Netherlands, following the introduction of MenC conjugate vaccines, the incidence of MenC disease decreased by 95%.[13] So far, MenC conjugate vaccines (either monovalent or combination formulations) have been introduced in several European countries, Australia, Canada, the United States of America (USA) and more recently in Brazil [14,15]; however there are variations in the schedules used as reviewed elsewhere.[14] In several countries, including Belgium, France, Germany, Italy, Portugal, the Netherlands and Australia, only a single dose of vaccine is administered to toddlers, usually at around 12–15 months of age. [16,17] In other countries where MenC conjugate vaccination is initiated in infancy, the number of primary doses also varies from one to three doses, usually administered at 1–2 month intervals between 2 and 8 months of age. Finally, Canada and several European countries, including the UK, Greece, Switzerland, Spain, Poland, Ireland, Iceland and Austria, have introduced adolescent booster doses of the vaccine.[16,17] The USA is unique in having introduced the quadrivalent meningococcal conjugate vaccine for adolescents only since 2005.[17]

Based on studies performed in the 1960s in the USA, Goldschneider et al. first demonstrated that serogroup-specific bacterial antibody protects against invasive meningococcal disease, and a serum bactericidal assay using human complement (hSBA) titer of ≥1:4 was shown to correlate with natural immunity and protection following immunization with purified capsular polysaccharide.[3,18] More recently, an SBA titer using rabbit complement (rSBA) of ≥1:8 has been validated as a correlate of protection against MenC disease using post-licensure vaccine effectiveness data from the UK.[12,19,20]

Of the three licensed monovalent MenC conjugate vaccines, two (Meningitec™ and Menjugate™) contain O-acetylated oligosaccharide derived from MenC capsular polysaccharide, conjugated to CRM197, while the other (NeisVac-C™) contains de-O-acetylated oligosaccharide conjugated to TT. In a review published in 2002, Lakshman and Finn concluded that no significant clinical difference between the three MenC conjugate vaccines was apparent;[21] however, subsequent studies have demonstrated several immunologically important differences. This manuscript has been prepared in response to an editorial request for an updated review on Meningitec vaccine. In this review, we have synthesized the available data on the immunogenicity, long-term persistence of bactericidal antibody, induction of immune memory and tolerability of Meningitec vaccine.

Search strategy
A search was carried out on PubMed and Medline using the following search terms: “Meningitec”; or “CRM197” in combination with “vaccine” and either “meningococcal”, “meningitis” or “MenC”. The authors screened and reviewed all abstracts from available publications and excluded any in which Meningitec™ was not included as a study or comparator vaccine. Any publication reporting any data regarding Meningitec™ vaccine was included. For any publication where this was unclear, the corresponding author was contacted for clarification of the specific meningococcal conjugate vaccine to which the publication referred. Related references from these publications were also identified and screened for inclusion.

Since rSBA is currently the universally accepted method of determining the immune response to MenC vaccines, these are the primary outcome measures discussed. In various studies, rSBA titers of >1:8 and ≥1:128 have been used as serological correlates of short-term and long-term protection, respectively, and in this review, data for both thresholds have been included wherever possible. Although the results of enzyme-linked immunosorbent assays (ELISAs) have been reported for some studies, these were a small minority, and the small numbers did not allow useful conclusions to be drawn, and these data have not be included.

Product description
Meningitec is a liquid vaccine, and each 0.5 ml dose contains 10 µg of MenC oligosaccharide linked to 15 µg of CRM197.[22] Polysaccharide purified from the culture of N. meningitidis strain C11 is cleaved into oligosaccharides and then coupled with CRM197 by reductive amination. The glycoconjugate is sterile filtered and compounded at 20 µg/ml of saccharide with aluminum phosphate at 1 mg/ml and then bottled in single-dose vials. On shaking the vial, the vaccine forms a homogeneous white suspension and is administered as an intramuscular injection.

NeisVac-C is also presented as a suspension, and each 0.5 ml dose contains 10 µg of MenC polysaccharide conjugated with 10–20 µg of TT, absorbed to 0.5 mg of aluminum hydroxide. [21] Menjugate, on the other hand, is presented as lyophilized powder (vaccine component) and a diluent syringe containing a suspension of aluminum hydroxide as the adjuvant. Each 0.5 ml of reconstituted vaccine dose contains 10 µg of MenC oligosaccharide conjugated with 12.5–25 µg of CRM197, absorbed to 1 mg of aluminum hydroxide.[21] All brands of MenC vaccine must be stored in a refrigerator to maintain a temperature of 2–8°C, but should not be frozen.[21,22] Manufacturer details of the vaccines are provided at the end of this review.

1. Immunogenicity
Data from several Phase II and III trials have shown that Meningitec is immunogenic in all age groups, including premature infants. A summary of the results of these trials is provided in Tables 1 and 2.
### Table 1. Summary of results from Phase II clinical trials of Meningitec

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Study design</th>
<th>Age and schedule of Meningitec administration</th>
<th>Vaccine group/comparison group</th>
<th>N&lt;sup&gt;a&lt;/sup&gt;</th>
<th>rSBA GMT (95% confidence interval)</th>
<th>% with rSBA ≥ 8 (95% confidence interval)</th>
<th>% with rSBA ≥ 128 (95% confidence interval)</th>
<th>Coadministered vaccines&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bramley et al. [23]</td>
<td>2001</td>
<td>Pilot and lot 1: double-blind RCT; lot 2 added as open-label RCT</td>
<td>2, 3 and 4 months</td>
<td>Pilot lot</td>
<td>60</td>
<td>555.1 (398.5, 773.3)</td>
<td>98% (92%, 100%)</td>
<td>–</td>
<td>DTwP-Hib&lt;sup&gt;c&lt;/sup&gt;, Oral polio vaccine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Manufacturing lot 1</td>
<td>61</td>
<td>472.9 (360.5, 620.2)</td>
<td>98% (92%, 100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Manufacturing lot 2</td>
<td>50</td>
<td>596.3 (387.5, 917.7)</td>
<td>98% (91%, 100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total (all lots)</td>
<td>171</td>
<td>535.3 (441.2, 649.5)</td>
<td>98% (95%, 100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borrow et al. [24]</td>
<td>2002</td>
<td>Sequential cohort enrolment clinical trial</td>
<td>2, 3 and 4 months</td>
<td>2 µg dose</td>
<td>49</td>
<td>1114.7 (779.2, 1594.7)</td>
<td>100%</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 µg dose</td>
<td>50</td>
<td>968.8 (661.6, 1418.6)</td>
<td>98%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>English et al. [25]</td>
<td>2000</td>
<td>Double-blind RCT</td>
<td>2, 3 and 4 months</td>
<td>Meningitec</td>
<td>58</td>
<td>1428.7 (1125.1, 1814.3)</td>
<td>100%</td>
<td>–</td>
<td>Tnvax, HibTITER, Oral polio vaccine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hepatitis B vaccine (Engerix B; control group)</td>
<td>59</td>
<td>2.9 (1.8, 4.9)</td>
<td>–</td>
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<tr>
<td>Collins et al. [26]</td>
<td>2005</td>
<td>Open-label, non-randomized 2-center, trial</td>
<td>2, 3 and 4 months</td>
<td>Premature infant group</td>
<td>59</td>
<td>506 (30.6, 836)</td>
<td>95%</td>
<td>90%</td>
<td>DTwP/Hib, Oral polio vaccine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Term infant group (control)</td>
<td>60</td>
<td>691 (467, 1023)</td>
<td>98%</td>
<td>92%</td>
<td></td>
</tr>
<tr>
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<td></td>
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<td>Result taken from a parallel RCT</td>
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<tr>
<td>Richmond et al. [27]</td>
<td>1999</td>
<td>Sequential cohort enrolment clinical trial</td>
<td>2, 3 and 4 months</td>
<td>2 µg dose</td>
<td>56</td>
<td>1102.9 (804, 1513)</td>
<td>100%</td>
<td>–</td>
<td>Tnvax, HibTITER</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 µg dose</td>
<td>53</td>
<td>1011 (702, 1455)</td>
<td>98%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Author [reference]</th>
<th>Year of publication</th>
<th>Study design</th>
<th>Age and schedule of Meningitec administration</th>
<th>Vaccine group/ comparison group</th>
<th>N</th>
<th>rSBA GMT (95% confidence interval)</th>
<th>% with rSBA ≥ 8 (95% confidence interval)</th>
<th>% with rSBA ≥ 128 (95% confidence interval)</th>
<th>Coadministered vaccinesb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slack et al. [28]</td>
<td>2001</td>
<td>Open-label, non-randomized trial</td>
<td>2, 3 and 4 months</td>
<td>Premature infant group</td>
<td>105</td>
<td>398 (298, 532)</td>
<td>99%</td>
<td>86%</td>
<td>- Infanrix-Hib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Term infant group (control)</td>
<td>54</td>
<td>380 (275, 526)</td>
<td>98%</td>
<td>78%</td>
<td></td>
</tr>
<tr>
<td>Rennels et al. [29]</td>
<td>2001</td>
<td>Double-blind RCT</td>
<td>2, 4 and 6 months</td>
<td>Meningitec</td>
<td>30</td>
<td>462.6 (315.3, 678.7)</td>
<td>100% (88.4%, 100%)</td>
<td>–</td>
<td>– Oral polio vaccine – DTwP/Hib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Booster dose at 12–15 months</td>
<td>Meningitec</td>
<td>48</td>
<td>2341.4</td>
<td>100 (92.8%, 100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Richmond et al. [30]</td>
<td>2001</td>
<td>Investigator-blinded RCT*</td>
<td>Single dose at 12–18 months (mean13.6 months)</td>
<td>Meningitec</td>
<td>70</td>
<td>141 (90, 222)</td>
<td>91%</td>
<td>–</td>
<td>Combination measles, mumps, rubella vaccine</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Menjugate</td>
<td>72</td>
<td>123 (78, 195)</td>
<td>92%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NeisVac-C</td>
<td>72</td>
<td>564 (406, 783)</td>
<td>100%</td>
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<tr>
<td>Burrage et al. [31]</td>
<td>2002</td>
<td>Investigator-blinded RCT*</td>
<td>Single dose at 3.5–6 years (school entry group) or 14.1–17.8 years (school leaver group)</td>
<td>Meningitec</td>
<td>58</td>
<td>2048 (1367, 3067)</td>
<td>–</td>
<td>–</td>
<td>Combination diphtheria and tetanus (DT or Td) vaccine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Menjugate</td>
<td>62</td>
<td>740 (454, 1207)</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NeisVac-C</td>
<td>31</td>
<td>1400 (763, 2569)</td>
<td>–</td>
<td>–</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(DT or Td, then MenC conjugate vaccine)</td>
<td>Meningitec</td>
<td>55</td>
<td>1898 (1,089, 3,311)</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Menjugate</td>
<td>51</td>
<td>1142 (655, 1990)</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NeisVac-C</td>
<td>28</td>
<td>4412 (3003, 6482)</td>
<td>–</td>
<td>–</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(MenC conjugate vaccine, then DT or Td)</td>
<td>Meningitec</td>
<td>56</td>
<td>1638 (991, 2710)</td>
<td>–</td>
<td>–</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Menjugate</td>
<td>63</td>
<td>877 (515, 1494)</td>
<td>–</td>
<td>–</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NeisVac-C</td>
<td>41</td>
<td>2191 (1342, 3577)</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(MenC conjugate vaccine with DT or Td)</td>
<td>Meningitec</td>
<td>56</td>
<td>1638 (991, 2710)</td>
<td>–</td>
<td>–</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Menjugate</td>
<td>63</td>
<td>877 (515, 1494)</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NeisVac-C</td>
<td>41</td>
<td>2191 (1342, 3577)</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Author [reference]</td>
<td>Year of publication</td>
<td>Study design</td>
<td>Age and schedule of Meningitec administration</td>
<td>Vaccine group/comparison group</td>
<td>N</td>
<td>rSBA GMT (95% confidence interval)</td>
<td>% with rSBA ≥ 8 (95% confidence interval)</td>
<td>% with rSBA ≥ 128 (95% confidence interval)</td>
<td>Coadministered vaccines[b]</td>
</tr>
<tr>
<td>--------------------</td>
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</tr>
<tr>
<td>Richmond et al. [32]</td>
<td>2000</td>
<td>Open-label, non-randomized trial</td>
<td>Single dose at 18–25 years (vaccine naïve group)</td>
<td>Meningitec</td>
<td>86</td>
<td>1336 (908,1966)</td>
<td>100%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Open-label RCT</td>
<td>Single booster dose at 18–25 years, 6 months after a primary dose of MACP (MACP primed group)</td>
<td>Meningitec booster (Primed with single dose of MACP 6 months prior)</td>
<td>83</td>
<td>663 (446, 987)</td>
<td>99%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Borrow et al. [33]</td>
<td>2001</td>
<td>Open-label, non-randomized trial</td>
<td>Single booster dose 7 months after a primary dose of MACP at 4–62 months (median 34 months)</td>
<td>Meningitec booster (Primed with single dose of MACP 7 months prior)</td>
<td>54</td>
<td>176.4 (95.7, 325.2)</td>
<td>–</td>
<td>–</td>
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</tr>
</tbody>
</table>

RCT = randomized control trial; rSBA = serum bactericidal assay using rabbit complement; GMT = geometric mean titer.

a Number of study participants with evaluable results.
b See list of vaccines in main article for antigens included in each coadministered vaccine.
c Combination diphtheria, tetanus, whole cell pertussis and Haemophilus influenzae type b vaccine.
d Subset of participants with SBA titers tested; Pneumococcal conjugate vaccine results published elsewhere.
e Laboratory assays were performed by blinded investigators.
f Combination meningococcal serogroups A and C polysaccharide vaccine.
<table>
<thead>
<tr>
<th>Author [reference]</th>
<th>Year of publication</th>
<th>Study design</th>
<th>Age and schedule of Meningitec administration</th>
<th>Vaccine group/comparison group</th>
<th>N&lt;sup&gt;a&lt;/sup&gt;</th>
<th>rSBA GMT (95% confidence interval)</th>
<th>% with rSBA ≥8 (95% confidence interval)</th>
<th>% with rSBA ≥128 (95% confidence interval)</th>
<th>Coadministered vaccines&lt;sup&gt;b&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td><strong>Phase III Trials</strong></td>
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</tr>
<tr>
<td>Knuf et al. [34]</td>
<td>2009</td>
<td>Combination of RCTs: some double-blind, some single-blind, some open-label</td>
<td>2 and 4 months (Menitorix administered at 2, 4 and 6 months)</td>
<td>Post dose 2</td>
<td>Meningitec</td>
<td>165</td>
<td>1299.8 (1082.0, 1561.5)</td>
<td>98.8% (95.7%, 99.9%)</td>
<td>97.0% (93.1%, 99.0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NeisVac-C</td>
<td>177</td>
<td>1474.2 (1263.3, 1720.4)</td>
<td>100% (97.9%, 100%)</td>
<td>97.2% (93.5%, 99.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Menitorix</td>
<td>168</td>
<td>501.8 (410.3, 613.6)</td>
<td>97.6% (94.0%, 99.3%)</td>
<td>89.3% (83.6%, 93.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Post dose 3</td>
<td>Meningitec (no dose 3)</td>
<td>126</td>
<td>665.2 (528.8, 836.8)</td>
<td>97.6% (93.2%, 99.5%)</td>
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<td></td>
<td></td>
<td></td>
<td>NeisVac-C (no dose 3)</td>
<td>138</td>
<td>1152.6 (958.4, 1386.3)</td>
<td>100% (97.4%, 100%)</td>
<td>97.1% (92.7%, 99.2%)</td>
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<tr>
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<td></td>
<td></td>
<td>Menitorix</td>
<td>137</td>
<td>1590.9 (1298.5, 1949.1)</td>
<td>100% (97.3%, 100%)</td>
<td>97.1% (92.7%, 99.2%)</td>
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<tr>
<td>Pace et al. [35]</td>
<td>2007</td>
<td>Open-label RCT</td>
<td>2, 3 and 4 months</td>
<td>Meningitec + Pediacel</td>
<td>117</td>
<td>1002.6 (833.8, 1205.6)</td>
<td>100% (96.9%, 100%)</td>
<td>99.1% (95.3%, 100%)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Menitorix + Infanrix-IPV</td>
<td>354</td>
<td>581.1 (514.7, 656.2)</td>
<td>99.2% (97.5%, 99.8%)</td>
<td>92.9% (89.8%, 95.4%)</td>
</tr>
</tbody>
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(continued)
<table>
<thead>
<tr>
<th>Author [reference]</th>
<th>Year of publication</th>
<th>Study design</th>
<th>Age and schedule of Meningitec administration</th>
<th>Vaccine group/comparison group</th>
<th>N</th>
<th>rSBA GMT (95% confidence interval)</th>
<th>% with rSBA ≥8 (95% confidence interval)</th>
<th>% with rSBA ≥128 (95% confidence interval)</th>
<th>Coadministered vaccines</th>
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</thead>
<tbody>
<tr>
<td>Tejedore et al. [36]</td>
<td>2006</td>
<td>Open-label, multicenter RCT</td>
<td>2, 4 and 6 months (NeisVac-C administered at 2 and 4 months)</td>
<td>Meningitec post dose 2</td>
<td>113</td>
<td>1355.5 (1075.0, 1709.2)</td>
<td>98.2%</td>
<td>97.3% (92.4%, 99.4%)</td>
<td>Infanrix hexa</td>
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<td></td>
<td></td>
<td>Meningitec post dose 3</td>
<td>114</td>
<td>1833.7 (1493.7, 2251.0)</td>
<td>99.1%</td>
<td>98.2% (93.8%, 99.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NeisVac-C</td>
<td>105</td>
<td>1187.2 (950.1, 1483.4)</td>
<td>100%</td>
<td>96.2% (90.5%, 99.0%)</td>
<td></td>
</tr>
<tr>
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<td></td>
<td>NeisVac-C + Hepatitis B vaccine (Engerix-B; at birth)</td>
<td>106</td>
<td>1542.9 (1282.2, 1856.5)</td>
<td>100%</td>
<td>98.1% (93.4%, 99.8%)</td>
<td>Infanrix penta/Infanrix-IPV</td>
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<tr>
<td>Tejedor et al. [37]</td>
<td>2004</td>
<td>Open-label, multicenter RCT</td>
<td>2, 4 and 6 months</td>
<td>Coadministration group</td>
<td>220</td>
<td>1372.6 (1196.7, 1574.4)</td>
<td>99.5% (97.5%, 100%)</td>
<td>99.1 (96.8, 99.9)</td>
<td>Infanrix hexa</td>
</tr>
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<td></td>
<td>Separate administration group</td>
<td>221</td>
<td>2257.1 (1964.4, 2593.5)</td>
<td>100% (98.3%, 100%)</td>
<td>99.5 (97.5, 100.0)</td>
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</tr>
<tr>
<td>Vesikari et al. [38]</td>
<td>2010</td>
<td>Phase IIIb, double-blind RCT</td>
<td>2, 4 and 6 months</td>
<td>Meningitec + oral rotavirus vaccine</td>
<td>184</td>
<td>1455.4 (1240.2, 1707.9)</td>
<td>–</td>
<td>–</td>
<td>Infanrix hexa</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Meningitec only</td>
<td>90</td>
<td>1769.1 (1374.3, 2277.5)</td>
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<tr>
<td>Vesikari et al. [39]</td>
<td>2011</td>
<td>Open-label RCT</td>
<td>Single dose at 12–19 months</td>
<td>Meningitec</td>
<td>121</td>
<td>212.3 (170.0, 265.2)</td>
<td>97.5%</td>
<td>70.2%</td>
<td>Combination measles, mumps, rubella, varicella vaccine</td>
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<tr>
<td>Booy et al. [40]</td>
<td>2011</td>
<td>Open-label multicenter RCT</td>
<td>Single dose at 12–18 months (mean 12.5 months)</td>
<td>Meningitec</td>
<td>98</td>
<td>621.0 (480.3, 802.9)</td>
<td>100%</td>
<td>90.8%</td>
<td>Combination measles, mumps, rubella vaccine</td>
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<td>Menitorix</td>
<td>281</td>
<td>482.8 (420.7, 554.2)</td>
<td>99.6%</td>
<td>87.9%</td>
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Table 2. (continued).

<table>
<thead>
<tr>
<th>Author [reference]</th>
<th>Year of publication</th>
<th>Study design</th>
<th>Age and schedule of Meningitec administration</th>
<th>Vaccine group/comparison group</th>
<th>N&lt;sup&gt;a&lt;/sup&gt;</th>
<th>rSBA GMT (95% confidence interval)</th>
<th>% with rSBA ≥8 (95% confidence interval)</th>
<th>% with rSBA ≥128 (95% confidence interval)</th>
<th>Coadministered vaccines&lt;sup&gt;b&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Diez-Domingo et al. [41]</td>
<td>2010</td>
<td>Open-label multicenter RCT</td>
<td>Single booster dose at 14–18 months following priming with Meningitec at 2, 4, and 6 months or NeisVac-C at 2 and 4 months</td>
<td>Meningitec primed and boosted</td>
<td>100</td>
<td>1746 (1378, 2213)</td>
<td>–</td>
<td>99.5% overall</td>
<td>– Hepatitis B vaccine - Infanrix-IPV+Hib/ Pentavac - Prevenar</td>
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<tr>
<td>Diez-Domingo et al. [41]</td>
<td>2010</td>
<td>Open-label multicenter RCT</td>
<td>Single booster dose at 14–18 months following priming with Meningitec at 2, 4, and 6 months or NeisVac-C at 2 and 4 months</td>
<td>Meningitec primed, NeisVac-C booster</td>
<td>107</td>
<td>2061 (1599, 2627)</td>
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<tr>
<td>Diez-Domingo et al. [41]</td>
<td>2010</td>
<td>Open-label multicenter RCT</td>
<td>Single booster dose at 14–18 months following priming with Meningitec at 2, 4, and 6 months or NeisVac-C at 2 and 4 months</td>
<td>NeisVac-C primed, Meningitec booster</td>
<td>86</td>
<td>6278 (4841, 8144)</td>
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<tr>
<td>Diez-Domingo et al. [41]</td>
<td>2010</td>
<td>Open-label multicenter RCT</td>
<td>Single booster dose at 14–18 months following priming with Meningitec at 2, 4, and 6 months or NeisVac-C at 2 and 4 months</td>
<td>NeisVac-C primed and boosted</td>
<td>81</td>
<td>6786 (5023, 9167)</td>
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<td>–</td>
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<tr>
<td>Diez-Domingo et al. [41]</td>
<td>2010</td>
<td>Open-label multicenter RCT</td>
<td>Single booster dose at 14–18 months following priming with Meningitec at 2, 4, and 6 months or NeisVac-C at 2 and 4 months</td>
<td>Primed with Meningitec</td>
<td>207</td>
<td>1903 (1600, 2262)</td>
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<td>–</td>
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<tr>
<td>Diez-Domingo et al. [41]</td>
<td>2010</td>
<td>Open-label multicenter RCT</td>
<td>Single booster dose at 14–18 months following priming with Meningitec at 2, 4, and 6 months or NeisVac-C at 2 and 4 months</td>
<td>Primed with NeisVac-C</td>
<td>167</td>
<td>6520 (5359, 7932)</td>
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**Phase IV Trial**

<table>
<thead>
<tr>
<th>Author [reference]</th>
<th>Year of publication</th>
<th>Study design</th>
<th>Age and schedule of Meningitec administration</th>
<th>Vaccine group/comparison group</th>
<th>N&lt;sup&gt;a&lt;/sup&gt;</th>
<th>rSBA GMT (95% confidence interval)</th>
<th>% with rSBA ≥8 (95% confidence interval)</th>
<th>% with rSBA ≥128 (95% confidence interval)</th>
<th>Coadministered vaccines&lt;sup&gt;b&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Southern et al. [42]</td>
<td>2009</td>
<td>Open-label RCT</td>
<td>2 and 3 months or 2 and 4 months</td>
<td>Meningitec</td>
<td>119</td>
<td>229 (176, 298)</td>
<td>98% (93%, 99%)</td>
<td>80% (72%, 87%)</td>
<td>– Prevenar – Pediacel</td>
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<tr>
<td>Southern et al. [42]</td>
<td>2009</td>
<td>Open-label RCT</td>
<td>2 and 3 months or 2 and 4 months</td>
<td>Menjugate</td>
<td>121</td>
<td>682 (546, 852)</td>
<td>99% (96%, 100%)</td>
<td>95% (90%, 98%)</td>
<td>– Prevenar – Pediacel</td>
</tr>
<tr>
<td>Southern et al. [42]</td>
<td>2009</td>
<td>Open-label RCT</td>
<td>2 and 3 months or 2 and 4 months</td>
<td>NeisVac-C</td>
<td>109</td>
<td>437 (354, 539)</td>
<td>99% (95%, 100%)</td>
<td>93% (86%, 97%)</td>
<td>– Prevenar – Pediacel</td>
</tr>
</tbody>
</table>

<sup>a</sup> Number of study participants with evaluable results.

<sup>b</sup> See list of vaccines in main article for antigens included in each coadministered vaccine.
1.1. Immune response to primary vaccination with Meningitec

1.1.1. Infants aged less than 12 months

Various primary MenC immunization schedules have been studied in infants, including two-dose schedules at either 2 and 3, or 2 and 4 months of age,[34,42] and three-dose schedules at either 2, 3 and 4 months of age.[23–28] or 2, 4 and 6 months of age.[36–38] Overall, at least 98% of full-term infants were demonstrated to achieve MenC rSBA titers ≥1:8 one month after priming, regardless of the immunization schedule used. MenC rSBA geometric mean titers (GMTs) varied according to vaccination schedule used.

1.1.1.1. Immune response after two-dose priming

At 5 months of age, one or two months after priming with Meningitec at 2 and 3 or 2 and 4 months of age, at least 98% of infants had MenC rSBA titers ≥1:8.[34,42] However, the proportion of those who had MenC rSBA titers ≥1:128 was lower in a study conducted in England (80% [95% confidence interval 72–87%]) [42] compared to infants participating in a study conducted in Germany, Spain and Poland (97% [93.1–99.0%]).[34] Similarly, infants in the Southern et al. trial had a lower MenC rSBA GMT compared to infants in the Knuf et al. study ([229 [176–298] versus 1299.8 [1082.0–1561.5]). The significant differences in results from these two studies may be related to coadministered vaccines (7-valent pneumococcal conjugate vaccine [PCV7, Prevenar™] plus Pediacel™ in the former, and Infanrix hexa™ plus 10-valent pneumococcal conjugate vaccine in the latter), or may be related to operational differences between the laboratories performing the SBA assays in each trial. Southern et al. compared the immunogenicity of Meningitec to that of the other MenC-CRM197 vaccine (Menjugate) and to MenC-TT (NeisVac-C) and demonstrated that irrespective of the vaccine used, more than 98% of all children achieved MenC rSBA titers ≥1:8 one month after completion of the primary schedule; however, over 95% of infants in the Menjugate and NeisVac-C-primered groups achieved MenC rSBA titers ≥1:128 compared to only 80% in the Meningitec group. They found significant differences in the MenC rSBA GMTs achieved, with the highest levels demonstrated in infants primed with Menjugate (682 [546–852]), compared to infants primed with NeisVac-C (437 [354–539]) or Meningitec (229 [176–298]).[42]

1.1.1.2. Immune response after three-dose priming

In one of the first MenC conjugate vaccine immunogenicity studies to be conducted in infants, Meningitec was shown to be safe and immunogenic when administered as a three-dose primary schedule to infants at 2, 3 and 4 months of age along with the routine UK childhood immunization schedule of the time.[25] In this double-blind, randomized controlled trial (RCT), all infants were shown to have MenC rSBA titers ≥1:8, one month following completion of the primary immunization schedule. MenC rSBA GMT at 5 months of age was 1428.7 (1125.1–1814.3). More recently, similar results were seen in a Phase III open-label, RCT conducted in the UK and Poland, in which almost all infants had MenC rSBA titers ≥1:8 one month after priming with Meningitec plus a combination diphtheria, tetanus, acellular pertussis, inactivated poliovirus and Haemophilus influenzae type b vaccine (DTaP/IPV/Hib, Pediacel™) compared to priming with a combination Hib–MenC–TT conjugate vaccine (Menitorix™) plus DTaP/IPV (Infanrix-IPV™).[35] However, more infants in the Meningitec-primed group achieved MenC rSBA titers >1:128 compared to the Hib–MenC–TT-primed group (99.1% [95.3–100%] versus 92.9% [89.8–95.4%]). In addition, MenC rSBA GMT was significantly higher in the Meningitec group compared to the Hib–MenC–TT group (1002.6 [833.8–1205.6] versus 581.1 [514.7–656.2]).[35]

Meningitec has also been shown to elicit a strong immune response in premature infants.[26,28] The immune response in premature infants was shown to be non-inferior to that in full-term vaccine recipients with 95–99% of premature infants across two trials achieving MenC rSBA titers ≥1:8 one month post-priming, compared to 98–100% of full-term infants. In addition, at least 86% of premature infants and 78% of full-term infants in these studies achieved MenC rSBA titers ≥1:128. In one trial, the MenC rSBA GMT in premature infants was lower than that in full-term infants (506 [30.6–836] versus 691 [467–1023]).[26] However, very similar MenC rSBA GMTs were seen in both groups in the other trial (398 [298–532] versus 380 [275–526]).[28]

Lot-to-lot variation in the immune response to Meningitec was not seen in a Phase II/III trial conducted in the UK using this primary schedule.[23] In addition, a lower dose of Meningitec (2 μg of MenC oligosaccharide) has been shown to be non-inferior to the standard dose (10 μg of MenC oligosaccharide) with respect to induction of bactericidal antibody in two RCTs, with 100% of infants in the low-dose groups and 98% of infants in the high-dose group achieving MenC rSBA titers ≥1:8. MenC rSBA GMTs were around 1000 in all children.[24,27]

Four studies have been conducted using Meningitec to prime infants at either 2, 4 and 6 months of age[36–38] or 3, 5 and 7[37] months of age, with serum samples taken 1 month following completion of the primary schedule at 7 or 8 months of age. Across these studies, ≥99% of infants had MenC rSBA titers ≥1:8, and ≥98% of infants had titers ≥1:128.[36–38] MenC rSBA GMTs ranged from around 1370 to 2260.[36–38] with the exception of a much lower rSBA GMT (462.6 [315.3–678.7]) reported in a double-blind RCT conducted in 30 infants in the USA in 1996.[29]

MenC rSBA GMT was shown to be higher in children who received Meningitec separately from other routine childhood immunizations (DTaP/IPV/Hib and hepatitis B [HepB] vaccine, [Infanrix Hexa] administered at 2, 4 and 6 months of age: Meningitec administered at 3, 5 and 7 months of age) compared to children who received both vaccines concomitantly at 2, 4 and 6 months of age, with post-primary GMTs of 2257.1 (1964.4–2593.5) at 8 months of age in the separately
administered group compared to 1372.6 (1196.7–1574.4) in the coadministration group.[37] This difference may be due to prior vaccination with a diphtheria-containing vaccine enhancing the immune response to Meningitec in the separate administration group, or coadministration of the two vaccines interfering with the immune response to Meningitec. Alternatively, the higher MenC rSBA GMT in the separate administration group may simply be a consequence of the slightly older age at vaccination in this group. Similar results were reported in another RCT where at 7 months of age, 1 month after completion of a three-dose priming schedule, the MenC rSBA GMT in infants who had received Meningitec was 1833.7 (1493.7–2251.0).[36] The rSBA GMTs were not significantly different 1 month after the second dose of vaccine in children who had received Meningitec or MenC–TT (1355.5 [1075.0–1709.2] and 1542.9 [1282.2–1856.5], respectively).

1.2.1. Immunogenicity of a booster dose of Meningitec following priming with a MenC conjugate vaccine

The immune response to Meningitec administered as a booster vaccine has been studied in three trials where children were previously primed with either Meningitec or MenC–TT as infants.[29,34,41] An open-label RCT conducted in Spain compared the immunogenicity and persistence of bactericidal antibody following administration of either Meningitec or MenC–TT at 14–18 months of age to children who had completed their primary immunizations with either three doses of Meningitec or two doses of MenC–TT before 8 months of age.[41] Overall, 99.5% of children achieved MenC rSBA titers ≥1:128 one month following the booster vaccines; however, MenC rSBA GMT following booster vaccination was higher in MenC–TT-primed children (6520 [5355–7932]) than in Meningitec-primed children (1903 [1600–2262]), irrespective of which vaccine was used for boosting. In addition, MenC rSBA GMT following booster vaccination with Meningitec was lower in children primed with Meningitec than in children primed with MenC–TT (1746 [1378–2213]) versus 6278 [4841–8144]), suggesting that use of the same conjugating protein for both primary and booster vaccines is less important than the specific vaccine used for priming. Potential confounders here are the different number of priming doses of vaccine used in the two groups (three doses of Meningitec compared to two doses of MenC–TT), based on evidence from studies that have demonstrated a greater antibody response to a booster dose of Hib–MenC–TT in children primed with one dose of either MenC–CRM197 (Menjugate) or MenC–TT, compared to children primed with two doses of MenC–CRM197.[43] In a smaller study, investigators in the USA demonstrated a similar MenC rSBA GMT (2341.4) 1 month following administration of Meningitec to toddlers aged 12–15 months, who had previously been primed with three doses of Meningitec at 2, 4 and 6 months of age,[29] to that reported by Diez-Domingo et al. In this study, all children achieved MenC rSBA titers ≥1:8 post-booster.

A large, multi-centered RCT compared coadministration of one of two different pneumococcal conjugate vaccines, with either three doses of Hib–MenC–TT at 2, 4 and 6 months, or two doses of MenC–TT or Meningitec at 2 and 4 months (plus a third dose at 7 months of age in Poland only) followed by a booster dose of the same MenC vaccine at 11–18 months of age.[34] All children were shown to have MenC rSBA titers ≥1:8, and at least 97.4% of children had MenC rSBA titers ≥1:128; however, MenC rSBA GMT was lower in the Meningitec-primed and boosted group (2779.6 [2198.5–3514.2]) compared to children primed and boosted with MenC–TT (4587.8 [3763.1–5593.2]) or Hib–MenC–TT (5099.2 [3940.4–6598.9]).[34] The third dose of Meningitec or MenC–TT administered to children in Poland during the
primary vaccination course did not appear to have any impact on booster responses.

1.2.2. Immunogenicity of a booster dose of Meningitec following priming with MACP vaccine

An RCT in adults reported a MenC rSBA GMT of 663 (446–987) 4–6 weeks after a booster dose of Meningitec in participants who had previously received a dose of MACP vaccine. This was significantly lower than the rSBA GMT after a single dose of Meningitec in adults who were vaccine-naïve (1336 [908–1966]). In addition, adults who had received two doses of MACP had lower levels of bactericidal antibody than those who had received only a single dose of the vaccine, demonstrating the immune hyporesponsiveness induced by meningococcal polysaccharide vaccines, which can be at least partly overcome by administration of a booster dose of a conjugate vaccine like Meningitec. Ninety-nine percent of adults primed with MACP and boosted with Meningitec achieved MenC rSBA titers ≥1:8 compared to 94% of those primed and boosted with MACP.[32]

An observational study also conducted in the UK reported a MenC rSBA GMT of 176.4 (95.7–325.2) one month following a booster dose of Meningitec administered to children between 12 and 69 months of age, who had been vaccinated with a dose of MACP 7 months prior (at a median age of 34 months).[33] When stratified by age, children who were at least 31 months old at the time of the Meningitec booster had a higher rSBA GMT compared to younger children (330.1 [183.2–594.8] versus 80.6 [27.1–239.9]); however, these results are significantly lower than those reported in the RCTs described in Section 2.2.1 above, probably related to immune hyporesponsiveness induced by prior polysaccharide vaccination in these children.

2. Persistence of immune response

Levels of bactericidal antibody have been shown to wane rapidly following both primary and booster immunizations with Meningitec and other MenC conjugate vaccines. The rate of decline is dependent on the type of vaccine used, the number of doses of vaccine and age at vaccination.

2.1. Persistence of MenC bactericidal antibody following primary infant immunization

Persistence of bactericidal antibody following infant priming with Meningitec has been shown to be poor, particularly following schedules that are completed by 4 months of age. The proportion of infants with MenC rSBA titers of ≥1:8 has been reported to be as low as 17% at a median age of 12.8 months, around 11 months following two-dose priming at 2–4 months of age,[44] but up to 85% at 13–14 months of age, around 7 months following three-dose priming at 2, 4 and 6 months of age.[45] The proportions of infants with MenC rSBA titers ≥1:128 in these two studies were 6% and 56%, respectively, and rSBA GMTs were also very different (3.3 [2.5–4.3] versus 120.5 [80.2–180.9], respectively).[44,45] The two studies are not directly comparable, since the timing from completion of primary immunizations to blood sampling is different (11 months versus 7 months); however, it is clear that age at primary vaccination is an important factor in persistence of bactericidal antibody prior to the administration of a booster vaccine. Within the range mentioned above, investigators in the USA reported a MenC rSBA GMT of 26.4 (15.7–44.3) in 48 toddlers aged 12–15 months, 6–9 months following three-dose priming at 2, 4 and 6 months of age,[29] compared to a post-primary rSBA GMT of 462.6 (315.3–678.7). The proportion of infants with MenC rSBA titers ≥1:8 had also waned from 100% (88.4–100%) to 79.2% (65.0–89.5%) over this time.

In an RCT comparing low-dose (2 μg) and high-dose (10 μg) Meningitec used for infant priming, persistence of MenC bactericidal antibody was shown to be slightly better in low-dose vaccine recipients. At around 14 months of age (10 months post-priming), 67% of the children in the low-dose group still had a MenC rSBA titer of ≥1:8, compared to 53% in the high-dose group. The rSBA GMTs were 21.5 (12.7–36.1) and 13.5 (7.3–25), respectively.[27] This suggests a dose-effect of priming on persistence of bactericidal antibody, a finding that has been reported in studies of other MenC conjugate vaccines.[43] This difference was no longer evident in the group of children who were followed-up to 4 years of age (up to 3.5 years post-priming), at which point 8% of the children in the low-dose group still had a MenC rSBA titer of ≥1:8, compared to 12% in the high-dose group. The rSBA GMTs were 2.6 (2.1–3.1) and 3.2 (1.9–5.5), respectively at 4 years of age.[24]

The type of vaccine used for priming is also important, with greater persistence of bactericidal antibody following priming with MenC–TT or Hib–MenC–TT vaccines in infancy compared to Meningitec priming. Tejedor et al. demonstrated a higher proportion of infants with MenC rSBA titers >1:8 at 13–14 months of age, around 7 months following three-dose priming at 2, 4 and 6 months of age in children receiving Hib–MenC–TT compared to Meningitec recipients (96.3% [89.6–99.2%] versus 85.4% [75.8–92.2%]), however, this may not be statistically significant given overlapping confidence intervals. The rSBA GMTs and proportion of infants with MenC rSBA titers ≥1:128 were also trending to be higher in the Hib–MenC–TT-primed group than Meningitec- or MenC–TT-primed groups.[45] Similarly, researchers in the UK and Poland reported a higher MenC rSBA GMT in children primed with three doses of Hib–MenC–TT at 2, 3 and 4 months of age compared to children who received the same schedule with Meningitec (61.3 [50.9–73.7] versus 38.6 [27.5–54.2]).[46] Both groups showed antibody waning compared to results available from 1 month post-priming,[35] however, the decline was more rapid in the Meningitec group. Finally, Borrow et al. demonstrated rapid waning of bactericidal antibody in the first year of life following two-dose priming with any of the three licensed MenC conjugate vaccines at 2–4 months of age; however, persistence was greatest in children primed with MenC–TT. The proportions of children with rSBA titers ≥1:8 and ≥1:128 were 2–3 times higher in the MenC–TT-primed group compared to the Meningitec-primed group (48% [35–60%] and 17% [9–28%], respectively, for rSBA ≥1:8 and 14%
[7–25%] and 6% [2–14%] for rSBA ≥1:128). MenC rSBA GMT for the MenC–TT-primed group was also higher at 12–14 months of age (8.7 [5.7–13.3]) compared to the Meningitec-primed group (3.3 [2.5–4.3]). Conversely, in a Spanish trial, pre-booster blood samples obtained from toddlers aged 14–18 months, 6–10 months following priming with either three doses of Meningitec or two doses of MenC–TT before 8 months of age, did not show a significant difference in the persistence of immune response between groups. Fewer than half of all children (44%) were still protected 10 months post-priming, with rSBA titers ≥1:8, with an overall rSBA GMT of 8.2 (5.8–11.6).[41]

### 2.2. Persistence of MenC bactericidal antibody following primary vaccination in older children and adults

Waning of MenC bactericidal antibody has been observed as early as 6 months following a single dose of Meningitec administered to toddlers aged 12–18 months, with a significant decline in the rSBA GMTs from 141 (90–222) one month post-vaccination to 51 (30–85).[30] In the absence of booster doses of vaccine, waning of bactericidal antibody continues throughout childhood and early adolescence, such that by 2 years after immunization, only around 40% of children have MenC rSBA titers ≥1:8, and this proportion declines to 15% after 10 years.[47,48] A longitudinal observational study of a cohort of children in the UK who had received a single dose of MenC conjugate vaccine as part of the nationwide catch-up immunization campaign in 1999–2001, demonstrated persistent waning of bactericidal antibody throughout this time. At least 87% of the cohort were known to have received Meningitec vaccine between 15 and 45 months of age. The value of rSBA GMT declined from 8.0 (6.5–9.9) to 3.3 (2.5–4.3) at 2 and 10 years following immunization, respectively.[47] An amalgamation of data from several trials is incorporated into Figure 1, demonstrating the waning of bactericidal antibody over time in children who were vaccinated with a single dose of Meningitec between 1 and 4 years of age.[30–40,47,48]

As with the infant studies described above, persistence of MenC bactericidal antibody is affected by the type of vaccine administered. In one RCT, 6 months following a dose of MenC conjugate vaccine at a mean age of 13.6 months, 75% of Meningitec recipients had an rSBA titer ≥1:8 compared to 86% of MenC–TT recipients, and rSBA GMTs were 51 (30–85) and 166 (99–281) in the two groups, respectively.[30] Similarly, 86.7% (81.9–90.7%) of the children who received a dose of Hib–MenC–TT had MenC rSBA titers ≥1:8 after around one year, compared to 76.4% (66.2–84.8%) of Meningitec recipients [40] in another trial. Moreover, investigators in this study reported a substantial waning of bactericidal antibody in the Meningitec group (nearly a 10-fold decrease in rSBA GMTs from 621.0 [480.3–802.9] to 63.8 [43.3–94.1] and to lesser extent in the Hib–MenC–TT group (fivetfold decrease in rSBA GMTs from 482.8 [420.7–554.2] to 91.7 [75.6–111.3]) over the same time period.[40] In a recent Australian observational study, 38.1% (15.4–60.8%) of 11–16-year-old adolescents had MenC rSBA titers ≥1:8 seven to eight years following a single dose of Meningitec compared to 23.8% (3.9–43.7) of children who had received Menjugate and 47.6% (40.4–54.8%) of MenC–TT recipients.[49] MenC rSBA GMT was also highest in the MenC–TT group (12.75 [9.47–17.15]) compared to the Meningitec (10.77 [3.70–31.33]) or Menjugate groups (5.75 [2.20–15.02]).

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**Figure 1. Waning of meningococcal serogroup C (MenC) bactericidal antibody over time in children vaccinated with a single dose of Meningitec at 1–4 years of age.**

Notes: Data amalgamated from several studies.[30–40,47,48]

- MenC rSBA geometric mean titers (GMT).
- Proportion (%) with MenC rSBA titers ≥1:8.
Several theories have been postulated to explain the differences outlined above in immunogenicity and persistence of bactericidal antibody noted between the TT- and CRM$_{197}$-conjugated MenC vaccines, including the suggestion that the TT carrier protein is inherently more immunogenic, or that similarities in the carrier protein used for priming and boosting may be important. In a recently published report, persistence of bactericidal antibody was documented after 12–14 years in a group of adolescents previously primed with a single dose of any of the three licensed MenC conjugate vaccines at 3–6 years of age.[50] Fifty-three percent (35–70%) of those primed with MenC–TT had SBA titers ≥1:8, compared to 42% (23–63%) in the Meningitec-primed group, and 24% (11–42%) in those primed with the other MenC–CRM$_{197}$ vaccine. MenC rSBA GMTs in each of the groups were 26 (10–64), 10 (4–22) and 5 (3–10), respectively. In this trial, adolescents were then randomized to receive a booster dose of a CRM$_{197}$- or TT-conjugate quadrivalent MenACWY (meningococcal serogroups A, C, W$_{135}$, and Y) vaccine. The results of the booster stage of the trial did not support either the suggestion that CRM$_{197}$-conjugated vaccines are inherently less immunogenic, nor that priming and boosting with the same carrier protein is always superior to priming and boosting with different carrier proteins.[50]

An additional key difference in the TT-conjugate MenC vaccine is its inclusion of de-O-acetylated oligosaccharide compared to O-acetylated oligosaccharide in the CRM$_{197}$-conjugate vaccines. Around 12–15% of MenC clinical isolates have been shown to lack O-acetyl groups in their polysaccharide capsule, [51,52] and antibodies generated in response to carriage, vaccination, and infection have been shown to be specific to the presence or absence of this moiety.[52] These findings raise the possibility of impaired MenC functional activity of vaccine-induced antibodies against heterologous isolates, which may affect immunogenicity assays, although the SBA assay appears to be less affected than ELISA-based assays.[30]

Several previous studies have suggested that the de-O-acetylated oligosaccharide may be more immunogenic than the O-acetylated oligosaccharide,[53–55] although this has not been confirmed in all studies.[56] Whether these differences are clinically relevant with respect to vaccine efficacy has not been determined. O-acetylation is unlikely to explain all the differences in immunogenicity, given that Hib–MenC–TT is also O-acetylated but shown to be more immunogenic than CRM$_{197}$-conjugated vaccines in some trials, and differences have been documented between Meningitec and Menjugate, both of which are CRM$_{197}$-conjugated and O-acetylated. As such, differences in the oligosaccharide chain length and the number of conjugation sites available may also influence the immunogenicity of conjugate vaccines.[57]

Age at vaccination has also been shown to be important for persistence of MenC bactericidal antibody beyond infancy. Researchers in Greece reported that 3.5 years after a single dose of Meningitec, the percentage of children with MenC rSBA titers of ≥1:8 was four times higher in the group who were vaccinated at older than 10 years compared to children who were vaccinated at less than 6 years of age (62.2% [48.1–76.4%] versus 14.1% [8.4–19.8%]).[58] Similarly, in the Australian study reported by Perrett et al., the MenC rSBA GMT was significantly lower 7–8 years after vaccination in adolescents who received any MenC conjugate vaccine at 2–4 years of age (6.89 [4.96–9.56]) compared with those who were vaccinated at 5–8 years of age (21.20 [14.0–32.1]).[49] Finally, in another observational study conducted in the UK, persistence of bactericidal antibody 5 years after receipt of a single dose of vaccine at 6–15 years was higher in children immunized at older ages, compared to children immunized at a younger age. This was true for any of the MenC conjugate vaccines, although the number of Meningitec recipients was too small to show a statistically significant difference within the subgroup.[59] Overall, persistence of immune response in these adolescents was better than that reported for children vaccinated as toddlers.[47,58] Five years after a dose of vaccine, rSBA GMT was 321.0 (199.1–517.5), and 86.3% (79.3–93.2%) of the 95 individuals who had received Meningitec had MenC rSBA ≥1:8.[59]

2.3. Persistence of MenC bactericidal antibody following booster vaccination

Persistence of MenC bactericidal antibody following a booster dose of Meningitec has been investigated in preschool children who had previously been primed with a dose of MACP vaccine at a median age of 34 months (range 4–62 months). Blood samples were available from 34 children one and six months after a booster dose of Meningitec and demonstrated a significant decline in the MenC rSBA GMT from 176.4 (95.7–325.2) to 81.7 (40.5–164.9).[33]

3. Immune memory

Following immunization (or infection), antigen concentrated in secondary lymphoid organs is able to activate a small proportion of mature naïve B-cells that are able to recognize it. These antigen-activated B-cells can then migrate to the periphery of the follicle, where they can engage in cognate interactions with T-helper cells, and subsequently migrate out into extra-follicular areas and proliferate down a pathway to terminal differentiation into short-lived antibody-secreting plasma cells.[60] Alternatively, the cell can move into the center of the B-cell follicle and proliferate to establish a germinal center within which affinity maturation occurs through the processes of clonal proliferation, somatic hypermutation and selection, producing antigen-specific memory B-cells.[61] There have been very few published reports of studies where MenC-specific memory B-cells have been directly measured following administration of MenC conjugate vaccines.[62,63] None of these studies used Meningitec vaccine.

Increases in antibody avidity have been used as a surrogate marker of immunological memory, since affinity maturation is characteristic of the immune response to T-cell-dependent antigens, resulting in the rapid production of high-affinity antibody on re-exposure to the antigen. Three studies reported on affinity maturation of MenC-specific IgG responses in children following
receipt of Meningitec vaccine, demonstrating significant increases in geometric mean avidity indices (GMAI) from 1 month to 6–9 months following vaccination.[24,30,33] This has been shown in children who had received a single dose of vaccine at a mean age of 13.6 months, as well as children who had received three doses of vaccine at 2, 3 and 4 months, and children who had received a single dose of vaccine 7 months following a dose of MACP polysaccharide vaccine at a median age of 34 months. In addition, MenC-specific IgG avidity indices have been shown to increase further following a challenge dose of MACP at around 20.5 months of age in children who had previously received a single dose of Meningitec at around 13.6 months,[30] or at around 4 years of age in children who had received three-dose Meningitec priming in infancy,[24] demonstrating the ability of Meningitec vaccine to selectively stimulate high-avidity memory B-cells. As would be expected, avidity maturation has been shown to occur following immunization with each of the three mono-valent MenC conjugate vaccines, with no significant differences between them [30], but has been shown not to occur following vaccination with the polysaccharide MACP vaccine, which induces a T-cell-independent immune response.[33]

More often, the ability of conjugate vaccines to prime for immune memory has been based on the demonstration of a fourfold or higher rise in antibody levels following a polysaccharide challenge. On this basis, clinical trials have demonstrated the ability of Meningitec to prime for memory in young children,[24,26,27,30] including premature infants.[26] In one report, administration of a MenC polysaccharide vaccine challenge at 12 months of age following three-dose priming at 2, 3, and 4 months of age resulted in almost a 20-fold increase in rSBA GMTs in premature and full-term infants in blood samples taken prior to and 2–4 weeks post-challenge (from 21.3 [11.7–38.6] to 407 [232–717] and from 37.3 [21.3–65.2] to 891 [568–1399], respectively).[26]

In an RCT comparing two different doses of Meningitec (10 µg and 2 µg) administered to infants at 2, 3 and 4 months of age, an anamnestic response to a 10 µg MenC polysaccharide challenge was demonstrated at 14 months of age and in a separate group of children at 4 years of age.[24,27] rSBA GMTs increased from 13.5 (7.3–25) and 21.5 (12.7–36.1) pre-booster in the high-dose and low-dose groups, respectively, to 256 (108–610) and 581 (322–2047) one month after the polysaccharide challenge administered at 14 months of age [27], and from 3.2 (1.9–5.5) and 2.6 (2.1–3.1) pre-booster in the high-dose and low-dose groups, respectively, to 93.1 (338.0–2568.0) and 2181.2 (975.9–4875.1) at 4 years of age.[24] A significantly greater rise was demonstrated in children in the low-dose group compared to the high-dose group at 14 months of age, and although this difference appeared to persist to 4 years of age, it was not statistically significant by this time. This inverse relationship between the dose of primary vaccine and response to a polysaccharide challenge correlates to a similar relationship with persistence of bactericidal antibody and suggests that lower-dose priming may favor induction of immune memory over plasma cell differentiation.

All three licensed MenC conjugate vaccines have been shown to induce immunological memory in toddlers. Six months after a single dose of MenC conjugate vaccine, 217 children at a mean age of 20.5 months were given a MACP vaccine challenge.[30] Pre- to post-challenge rSBA GMTs increased by 19-fold in children primed with Meningitec, from 51 (30–85) to 979 (686–1400). However, post-challenge rSBA GMTs were significantly lower in the Meningitec-primed group compared to children primed with MenC–TT, with a greater relative increase in rSBA GMT seen in children primed with MenC–TT (from 166 [99–289] to 5272 [3483–7980]).[30] This suggests that immunological mechanisms involved in priming for memory occur differently following vaccination with the different MenC conjugate vaccines.[60] The production of germinal centers may be less efficient following Meningitec priming compared to other MenC conjugate vaccines used for priming. This has potential consequences on levels of bactericidal antibody produced following booster vaccination, and persistence of antibody over time, as described in Sections 2.2.1 and 3 above.

Long-term persistence of bactericidal antibody following booster vaccination may simply be a function of the height of the post-booster antibody response, or may also be related to how different vaccines affect the various B-cell populations during priming.[60,61] Several RCTs have demonstrated poor persistence of bactericidal antibody following booster immunizations in children previously primed with Meningitec compared to those primed with other MenC conjugate vaccines.[44,46,64] A Phase III open-label RCT conducted in the UK and Poland showed that 6 weeks following a booster dose of Hib–MenC–TT at 12 months of age, the proportion of toddlers previously primed with Hib-MenC–TT at 2, 3 and 4 months of age achieving MenC rSBA titers ≥1:8 or ≥1:128 was higher than among those previously primed with Meningitec (99.1% [97.5–99.8%] versus 95.6% [90.1–98.6%] and 97.7% [95.5–99.0%] versus 86.0% [78.2–91.8%], respectively).[46] Furthermore, toddlers in the Hib-Men-TT-primed group had a 36-fold increase in their MenC rSBA GMT from pre-to post-booster time-points (from 61.3 [50.9–73.7] to 2193.7 [1881.1–2558.1]) compared to only a 12-fold increase in the Meningitec-primed group (from 38.6 [27.5–54.2] to 477.9 [357.3–639.2]).[46] This was despite higher bactericidal antibody levels at 5 months of age (1 month following the primary immunizations) in children primed with Meningitec compared to those primed with Hib–MenC–TT [35] and suggests a differential effect on plasma cell differentiation and antibody production versus memory B-cell priming by the two different vaccines. In a follow-on study of these children at 5 years of age, persistence of bactericidal antibody for 4 years following the toddler booster dose of Hib–MenC–TT was better in children previously primed in infancy with Hib–MenC–TT compared to those who had received Meningitec priming.[64] Children in the Hib–MenC–TT-primed group had more than a twofold higher MenC rSBA GMT than children in the Meningitec-primed group (30.4 [22.9–40.4] versus 11.3 [7.7–16.5]). Although the proportion of children with MenC rSBA titers ≥1:8 was not significantly different between groups (59.3%
[52.0–66.3%] and 44.8% [31.7–58.5%, respectively], the proportion of children with MenC rSBA titers ≥1:128 was 3.5 times higher in the Hib-MenC–TT-primered group than in the Meningitec–primed group (29.9% [23.5–36.9%] versus 8.6% [2.9–9.0%]).[47]

Similarly, investigators comparing the effect of priming with each of the three MenC conjugate vaccines in infancy followed by a booster dose of Hib–MenC–TT at 12–14 months of age demonstrated higher post-booster bactericidal antibody levels in children primed with MenC–TT (2085.7 [1475.6–2948.0]) compared to children primed with Meningitec (368.4 [253.7–534.9]) or Meningitec (467.3 [329.8–662.1]). After 2 years, children in the MenC–TT–primed group continued to have a higher rSBA GMT (9.0 [5.0–16.0]) than children primed with Meningitec (3.6 [2.4–5.6]) or Meningitec (4.3 [2.8–6.7]). The proportion of children in each group who still had MenC rSBA titers ≥1:8 two years post-booster was 43%, 23% and 22%, respectively.[44]

4. Effect of Meningitec on the immune response to coadministered vaccines

In most clinical trials, Meningitec has been shown not to have a clinically significant negative impact on the immune response to coadministered vaccines, including Infanrix hexa,[34,37,45] Pediacel[42] and pneumococcal conjugate vaccines.[34,42] MenC conjugate vaccine carrier protein effects on the immune responses to diphtheria and tetanus components of other vaccines have been demonstrated in several trials.[31,34,37,45] In one RCT, separate administration of Infanrix hexa and Meningitec in a three-dose primary schedule resulted in higher anti-diphtheria antibody levels compared to coadministration of the two vaccines.[37] Conversely in another trial, coadministration of Infanrix hexa and MenC–TT vaccine to infants resulted in higher anti-tetanus antibodies, whereas there was no significant impact on the levels of anti-diphtheria antibody with coadministration of Infanrix hexa and Meningitec.[34] In older children and adolescents, prior or coadministration of either of the MenC-CRM197 vaccines with DT/Td vaccine resulted in higher anti-diphtheria antibody levels, whereas this effect was only evident for anti-tetanus antibody levels with coadministration of MenC–TT in adolescents and with prior administration of MenC–TT to school-aged children.[31] In infants receiving primary immunizations at 2, 4 and 6 months of age with Infanrix hexa and either Meningitec or MenC–TT, persistence of anti-tetanus antibody to 12 months of age was shown to be significantly better in the MenC–TT–primed group.[45]

The immune response to the Hib component of childhood combination vaccines such as Infanrix hexa and Pediacel has been shown to be reduced when coadministered with Meningitec or Meningitec compared to TT-conjugated MenC vaccines in several studies. When DTaP/IPV/Hib/HepB (Infanrix hexa) was coadministered with either Meningitec or MenC–TT, or when DTaP/IPV/Hib (Infanrix penta) was coadministered with Hib–MenC–TT, post-primary anti-polysialyl ribitol phosphate (PRP) antibody levels were higher in children in the MenC–TT and Hib–MenC–TT groups compared to the Meningitec group.[34] In this study, post-booster anti-PRP levels (following a toddler booster dose of Hib–MenC–TT) were also higher in the Hib–MenC–TT–primed children compared to the Meningitec– and MenC–TT–primed children. Similarly, after three doses of DTaP/IPV/HepB (Pediacel) and two doses of one of the three licensed MenC conjugate vaccines administered to infants aged 2, 3 and 4 months, post-primary anti-PRP antibody levels were significantly higher in children primed with MenC–TT compared to children primed with either of the CRM197-conjugated vaccines.[42] Another trial comparing MenC–TT to Meningitec reported similar findings with respect to post-primary anti-PRP antibody responses.[65] Furthermore, persistence of anti-PRP antibody to 14 months of age has been shown to be better in children primed with Infanrix hexa and MenC–TT, or Infanrix penta and Hib–MenC–TT, compared to children primed with Infanrix hexa and Meningitec, with significantly higher anti-PRP antibody levels in the MenC–TT–primed group compared to the Meningitec–primed group 1 month after a toddler booster dose of Hib–MenC–TT.[45] The Hib component of these combination vaccines is conjugated to TT.

Conversely, when either Hib–MenC–TT or Meningitec plus a monovalent conjugate Hib vaccine (Hib-TT, Hiberial™) were administered to toddlers aged 12–17 months who had previously received either two doses of a Hib-outer membrane protein-containing vaccine or three doses of a DTaP/Hib-TT-containing vaccine, anti-PRP antibody levels were higher 1 month after vaccination in the Meningitec plus Hib-TT group, compared to the Hib–MenC–TT group.[40] However, this difference did not persist at 12 months after vaccination. In addition, in infants receiving a three-dose primary immunization schedule with DTaP/IPV/Hib/HepB, there were no significant differences in the post-primary anti-PRP antibody levels in children who had received coadministration of Meningitec compared to those who had received Meningitec at separate visits 1 month apart.[37] Finally, post-primary anti-PRP concentrations were higher when a Hib-CRM197 vaccine was used in the same schedule as Meningitec compared to a HepB control vaccine.[25]

Considering also the finding that prior immunization with a TT-containing vaccine reduced the immune response to MenC–TT whereas prior immunization with a diphtheria-containing vaccine did not affect the response to Meningitec,[31] the results of these studies show that the effect of different carrier proteins on the immune response to conjugate vaccines is unclear. A carrier dose-related effect has been demonstrated in a meta-analysis which found that with total CRM197 dose of approximately 50 μg, a trend toward lower MenC SBA GMTs was observed following coadministration of MenC–CRM197 and other CRM197-based conjugate vaccines.[60] In contrast, no such dose-related effect has been clearly identified with respect to the total TT dose and anti-PRP response to Hib-TT vaccines.[66] Evidence from other conjugate vaccines is also contradictory. Concomitant primary immunization of infants with a TT-conjugated pneumococcal
vaccine and a Hib-TT-containing vaccine has been reported to result in lower anti-PRP responses, an effect termed “carrier-induced epitopic suppression”.[67] Thus, inhibitory or enhancing effects between conjugate vaccines may be due to a combination of factors, including the timing of coadministered vaccines, the total dose of the various antigens and carrier proteins and also the specific characteristics of the polysaccharide.[68] The reader is referred to two recent reviews that have highlighted the complex interactions between concurrently administered conjugate vaccines.[66,69] At present, no single theory accurately predicts the interactions between various conjugate vaccines and thus various regimens must be evaluated on an empirical basis.[69]

5. Safety and reactogenicity

*Meningitec* has been shown to be safe and well-tolerated across all age groups.[23,30–36,40,70,71] including premature infants.[23,26,27] The reactogenicity profile of *Meningitec* is similar to or better than other routinely administered childhood vaccines, including PCV7, combination measles, mumps and rubella vaccine, DTap/Hib, DTwP/Hib (combination vaccine with whole cell pertussis) and DTap/IPV/Hib/HepB vaccines.[23,27,29,37,39] Specifically, rates of local and systemic reactions, and in particular rates of severe (grade 3) reactions, associated with *Meningitec* are generally similar to those occurring with other monovalent and combination MenC conjugate vaccines.[18,29,35,36,39,40] In various clinical trials, fever has been reported to occur in 4.5–14.5% of vaccine recipients after each dose of *Meningitec* vaccine.[27,36,37] Severe (grade 3) local or systemic reactions have been reported to occur after fewer than 4% of doses.[27,36,37] In addition, coadministration of Meningitec with DTap/IPV/Hib/HepB vaccines to infants did not result in a greater number of adverse reactions when compared to separate administration of the vaccines.[37]

In a large RCT conducted in California, safety data available on a total of almost 19,000 children who received at least one dose of *Meningitec* vaccine, administered at 2, 4 and 6 months of age, followed by a booster dose at 12–15 months of age did not reveal any serious adverse events related to vaccination.[71] Injection site redness occurred in less than 10% after each dose, and swelling and tenderness occurred in less than 7% and 18%, respectively. Severe (grade 3) redness and swelling occurred in up to 1.3% and 0.3% of doses, respectively. These rates were similar to reactions occurring at the injection sites of PCV7 and DTap vaccines. Fever occurred in up to 17% after each dose of *Meningitec* when coadministered with DTap and other routine immunizations, compared to up to 24% in children who received PCV7 with DTap and other routine immunizations. Fever >39°C occurred in up to 1.7% of vaccine recipients in the *Meningitec* group and up to 2.5% of the PCV7 group after each dose.

6. Efficacy and effectiveness

Estimates of efficacy and effectiveness have been calculated following the introduction of routine and catch-up immunization campaigns with MenC conjugate vaccines in the UK, Canada and Spain. No data are available for estimates of vaccine efficacy or effectiveness for *Meningitec* vaccine specifically. Publications from Spain and the UK incorporate combined data on all three licensed MenC conjugate vaccines. In particular, in the UK, *Meningitec* was widely used during the catch-up campaigns in 1999–2001; thus, estimates for vaccine efficacy and effectiveness from the UK are likely to largely reflect that for *Meningitec*.

In the UK, short-term vaccine efficacy was estimated as 97% (77–99%) for teenagers aged 15–17 years and 92% (65–98%) for toddlers aged 1–2 years 9 months after introduction of MenC conjugate vaccines.[72] This estimate was based on a population screening method using cases of MenC disease confirmed by the Public Health Laboratory Service Meningococcal Reference Unit in age groups targeted for immunization and data on vaccine coverage rates provided by child health departments. Subsequently, a case control study confirmed similarly high vaccine effectiveness (VE) in 15–19-year-olds within 2 years of immunization (93% [39–99%]).[73]

Enhanced disease surveillance in Spain and the UK in the 4 years after introduction of these vaccines allowed long-term VE to be calculated.[73,74] In both countries, high short-term VE estimates were determined in all age groups, including infants (>93%); however, there was a rapid decline in VE beyond 1 year after vaccination.[73,74] A greater decline in VE was noted in infants vaccinated according to routine schedules (2, 4 and 6 months in Spain or 2, 3 and 4 months in the UK), compared to older children vaccinated as part of catch-up campaigns. Updated post-licensure surveillance data from the UK up to 9 years following vaccine introduction provided an overall VE estimate of between 83% and 97% in each age group targeted for immunization.[12] VE in infants immunized with two or three doses of vaccine between 2 and 4 months of age was shown to decline from 97% (91–99%) within 1 year of vaccination to 68% (63–90%) beyond 1 year. A statistically significant decline in VE was not seen in older age groups.

In part based on the evidence for rapidly declining VE beyond a year after infant immunizations, booster doses of MenC conjugate vaccines were introduced for toddlers in both the UK and Spain. Revised estimates of VE from Spain up to 12 years following introduction of vaccines demonstrated increased VE and reduced loss of VE over time with the introduction of the booster vaccine (decline in VE from 97.5% to 81.4% in infants vaccinated according to a three-dose primary schedule, versus from 99.8% to 89.1% in infants who had received a three-dose primary schedule as well as a toddler booster dose of vaccine).[75] Increasing age at vaccination in catch-up campaigns was shown to also result in higher VE and reduced loss of VE over time.

7. Conclusions

The CRM₁₉₇-conjugated MenC vaccine *Meningitec* is safe and immunogenic in all age groups, producing MenC rSBA titers above the threshold for protection in almost all recipients. It has also shown to induce immunologic memory in infants and
toddlers; however, it appears to be less efficient at doing so than the TT-conjugated MenC vaccines. Consequently, persistence of bactericidal antibody and response to subsequent MenC booster vaccine doses are reduced following administration of Meningitec compared to that following administration of TT-conjugated MenC vaccines. The exact role that the different carrier proteins play in the immune response to conjugate vaccines and coadministered vaccines is not completely understood.

8. Expert commentary
Three MenC conjugate vaccines were first licensed in the UK in 1999 based solely on immunogenicity and safety data. Meningitec is one of two CRM197-conjugated vaccines shown to be immunogenic and well-tolerated in all age groups, including premature infants. Post-licensure effectiveness data from the UK and Spain demonstrated that the introduction of Meningitec and other MenC conjugate vaccines was effective at preventing disease in both vaccinated an unvaccinated cohorts, and in reducing carriage of MenC. In addition, induction of immune memory has been demonstrated following priming of infants and toddlers with Meningitec.

However, even in previously primed adults, serum antibody responses to meningococci are only detectable 4 days after exposure to a polysaccharide challenge.[76] Given the rapidity of invasion, the anamnestic response may be too slow to protect against meningococcal disease, and direct protection of individuals is largely dependent on sustained circulating bactericidal antibodies.[77] Unfortunately, waning of vaccine-induced bactericidal antibody occurs following primary and booster MenC conjugate vaccines, more rapidly in infants than in older children and adults. This explains the rapid waning of VE beyond 1 year after infant immunization, which has been demonstrated.

With specific reference to Meningitec, the results of several comparative trials have highlighted differences in the immunologic profile of this vaccine compared to other licensed MenC conjugate vaccines, in particular MenC–TT and HibMenC–TT. Despite its ability to induce MenC rSBA titers above the threshold for protection in almost all recipients, the height of the antibody response associated with Meningitec is often less than that of the TT conjugate vaccines, with lower GMTs reported for Meningitec recipients in comparative studies, when administered either as a primary or booster vaccine. Subsequently, persistence of bactericidal antibody following Meningitec is not as good as that with the TT conjugate vaccines. In addition, priming for immune memory appears to be less efficient with Meningitec compared to these other vaccines. Taken together, these data suggest a less favorable immunologic profile associated with Meningitec compared to TT-conjugated MenC vaccines in particular. Several hypotheses have been suggested to explain some of these differences, mainly related to the carrier proteins used. However, the effect of different carrier proteins on the immune response to conjugate vaccines remains unclear and may relate to a combination of factors, such as the timing of coadministered vaccines, the total dose of the various antigens and carrier proteins and also the specific characteristics of the polysaccharide used in the vaccine, including the size of oligosaccharide chains linked to the particular carrier protein and O-acetylation of the oligosaccharide.

It is possible that these immunological differences may not be clinically relevant in countries that have well-established MenC conjugate vaccine immunization programs, particularly in places where adolescent booster doses of vaccine have also been introduced, where the rates of MenC carriage and transmission are currently low. However, in countries that are either considering introducing MenC conjugate vaccines into the national schedule, or where rates of MenC disease and carriage are still relatively high, Meningitec is unlikely to have a major role in the future.

9. Five-year view
In addition to highlighting important differences between the MenC conjugate vaccines that have implications for the optimal design of childhood immunization schedules, the results of comparative trials have raised many interesting questions regarding the ability of conjugate vaccines to prime the immune system, particularly in infants. Further investigation of these questions is likely to enhance our understanding of the immune system, leading to the development of better vaccines in the future. Specifically, questions regarding the induction of immune memory according to dose and vaccine used for priming, as well as the effect of different carrier proteins, remain unanswered.

From a practical perspective, with the development of new vaccines and their introduction into already crowded childhood immunization schedules, it may become increasingly important to develop combination vaccines that retain adequate immunogenicity, reactogenicity and effectiveness compared to separately administered or coadministered vaccines. The more recently licensed quadrivalent MenACWY conjugate vaccines are likely to gain more widespread use in the future to broaden the coverage of protection against meningococcal disease beyond serogroup C. In the UK, the Joint Committee on Vaccination and Immunization has recently recommended the introduction of an adolescent booster of MenACWY conjugate vaccine from August 2015. Ongoing study of antibody persistence following immunization schedules that incorporate both monovalent and quadrivalent meningococcal vaccines will be necessary.

Vaccines
Meningitec – CRM197-conjugated MenC vaccine, currently manufactured by Pfizer Inc, New York, USA.
Menjugate – CRM197-conjugated MenC vaccine, manufactured by Novartis Vaccines and Diagnostics, Basel, Switzerland.
NeisVac-C – TT-conjugated MenC vaccine, manufactured by Baxter International Inc, Illinois, USA.
Menitorix – TT-conjugated combination Hib and MenC vaccine, manufactured by GlaxoSmithKline Biologicals, Rixensart, Belgium.
**Pediacel** – diphtheria and tetanus toxoids, acellular pertussis, inactivated poliovirus and conjugated *Haemophilus influenzae* type b combination vaccine, manufactured by Sanofi Pasteur, Lyon, France.

**Infanrix hexa** – diphtheria and tetanus toxoids, acellular pertussis, inactivated poliovirus, conjugated *Haemophilus influenzae* type b and recombinant hepatitis B combination vaccine, manufactured by GlaxoSmithKline Biologicals, Rixensart, Belgium.

**Infanrix pentax/Pediarix** – diphtheria and tetanus toxoids, acellular pertussis, inactivated poliovirus and recombinant hepatitis B combination vaccine, manufactured by GlaxoSmithKline Biologicals, Rixensart, Belgium.

**Infanrix-IPV** – diphtheria and tetanus toxoids, acellular pertussis and inactivated poliovirus, manufactured by GlaxoSmithKline Biologicals, Rixensart, Belgium.

**Infanrix-IPV+Hib** – diphtheria and tetanus toxoids, acellular pertussis, inactivated poliovirus and conjugated *Haemophilus influenzae* type b combination vaccine, manufactured by GlaxoSmithKline Biologicals, Rixensart, Belgium.

**Trivax** – diphtheria and tetanus toxoids and killed whole-cell *Bordetella pertussis* combination vaccine, manufactured by GlaxoSmithKline Biologicals (Glaxo Wellcome), Rixensart, Belgium.

**Prevenar/Prevnar** – CRM197-conjugated heptavalent pneumococcal vaccine against serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, manufactured by Pfizer Inc, New York, USA.

**Hiberix** – TT-conjugated *Haemophilus influenzae* type b vaccine, manufactured by GlaxoSmithKline Biologicals, Rixensart, Belgium.

**HibTITER** – CRM197-conjugated *Haemophilus influenzae* type b vaccine, manufactured by Pfizer Inc, New York, USA.

**Engerix B** – recombinant hepatitis B vaccine, manufactured by GlaxoSmithKline Biologicals, Rixensart, Belgium.

### Key issues

- **Meningitec** is a CRM197-conjugated MenC vaccine, shown to be immunogenic and well-tolerated in all age groups, including premature infants, inducing MenC bactericidal antibody titers above the threshold for protection in almost all recipients.

- Post-licensure effectiveness data from the UK and Spain have demonstrated that introduction of Meningitec and the other MenC conjugate vaccines was effective in preventing disease in both vaccinated and unvaccinated cohorts, and in reducing carriage of MenC.

- The height of the antibody response and persistence of bactericidal antibody following administration of Meningitec is reduced compared to that following administration of TT-conjugated MenC vaccines.

- Meningitec has also been shown to induce immunologic memory in infants and toddlers; however, it appears to be less efficient in doing so than the TT-conjugated MenC vaccines, leading to a less robust immune response to booster doses of vaccine.

- The exact role that different carrier proteins play in the immune response to conjugate vaccines and coadministered vaccines is not completely understood.

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Meningitec vaccine against meningitis

Drug Profile


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SECTION B: CROSS-SECTIONAL SURVEYS

Chapter 3: Vaccine Uptake and Factors that Affect it

Vaccination policies vary between vulnerable populations and depend on country- and context-specific factors e.g. presence of a recent outbreak [34, 84-86]. Among all these, the Hajj pilgrimage is a noticeable circumstance in which a vaccination policy has been sustained and enforced over almost 20 years. The Hajj provides a mix of high-risk settings and populations: mass gathering, crowded settings and travellers from all around the globe including pilgrims from countries in the African meningitis belt.

The current meningococcal vaccination policy was declared in 2002, and it mandates vaccination for all pilgrims and workers who serve them during Hajj. The vaccine must be received at least 10 days before attending for Hajj, and no more than three years prior (for the plain polysaccharide vaccine) or five years (for the conjugate vaccine).

Since the policy is well-enforced among overseas pilgrims and vaccine uptake is better-studied [87-91] compared to domestic pilgrims and workers, this section aims to assess this policy in terms of vaccine uptake and factors affecting its acceptance among two key groups in Hajj: domestic pilgrims and health care workers.
3.1 Meningococcal vaccine uptake among Hajj pilgrims


What is the context?

- Meningococcal vaccination is mandatory for both overseas (since 1988) and domestic (since 2002) Hajj pilgrims.
- The only available report on vaccine uptake among domestic Hajj pilgrims is outdated and shows a low coverage.

What is new?

- A cross-sectional survey conducted during peak of Hajj to determine vaccine uptake among domestic Hajj pilgrims and its influencing factors.

What is the impact?

- There is a need for certain measures to increase awareness of and facilitate access to meningococcal vaccines in order to improve acceptance and uptake.
Meningococcal Vaccine for Hajj Pilgrims: Compliance, Predictors, and Barriers

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Abstract: Background: Major intercontinental outbreaks of invasive meningococcal disease associated with the Hajj occurred in 1987, 2000, and 2001. Mandatory meningococcal vaccination for all pilgrims against serogroups A and C and, subsequently, A, C, W, and Y controlled the epidemics. Overseas pilgrims show excellent adherence to the policy; however, vaccine uptake among domestic pilgrims is suboptimal. This survey aimed to evaluate meningococcal vaccine uptake among Hajj pilgrims and to identify key factors affecting this. Methods: An anonymous cross-sectional survey was conducted among pilgrims in Greater Makkah during the Hajj in 2017–2018. Data on socio-demographic characteristics, vaccination status, cost of vaccination, and reasons behind non-receipt of the vaccine were collected. Results: A total of 509 respondents aged 13 to 82 (median 33.8) years participated in the survey: 86% male, 85% domestic pilgrims. Only 389/476 (81.7%) confirmed their meningococcal vaccination status; 64 individuals (13.4%), all domestic pilgrims, did not receive the vaccine, and 23 (4.8%) were unsure. Among overseas pilgrims, 93.5% certainly received the vaccine (6.5% were unsure) compared to 80.9% of domestic pilgrims (p < 0.01). Being employed and having a tertiary qualification were significant predictors of vaccination adherence (odds ratio (OR) = 2.2, 95% confidence interval (CI) = 1.3–3.8, p < 0.01; and OR = 1.7, CI = 1–2.5, p < 0.05, respectively). Those who obtained pre-Hajj health advice were more than three times as likely to be vaccinated than those who did not (OR = 3.3, CI = 1.9–5.9, p < 0.001). Lack of awareness (63.2%, 36/57) and lack of time (15.8%, 9/57) were the most common reasons reported for non-receipt of vaccine. Conclusion: Many domestic pilgrims missed the compulsory meningococcal vaccine; in this regard, lack of awareness is a key barrier. Being an overseas pilgrim (or living at a distance from Makkah), receipt of pre-Hajj health advice, and employment were predictors of greater compliance with the vaccination policy. Opportunities remain to reduce the policy–practice gap among domestic pilgrims.
Keywords: Hajj; meningococcal disease; vaccine uptake; pre-travel health advice

1. Introduction

Hajj is a large annual mass gathering that attracts more than two million Muslims from around the world to congregate within confined areas in Makkah, Saudi Arabia. A highly crowded and congested environment during Hajj amplifies risks associated with mass gatherings, including transmission of respiratory organisms, notably Neisseria meningitidis [1,2].

*Neisseria meningitidis* is associated with a substantially high rate of carriage (up to 86%) in crowded and closed populations, which resulted in large intercontinental outbreaks of invasive meningococcal disease during Hajj [3]. Following the Hajj in 1987, an intercontinental Hajj-related outbreak of meningococcal serogroup A (MenA) disease led to approximately 2000 cases [4], and its subsequent introduction into the African meningitis belt affected around 70,000 people [5]. Furthermore, in 2000 to 2001, a large outbreak of meningococcal disease resulted in at least 47 deaths, including 11 deaths in the United Kingdom, and affected no fewer than 2400 people in several countries throughout Asia, Africa, Europe, and North America. Serogroup W (MenW; a serogroup that was not previously known to cause large epidemics) sequence type 11 was responsible for over half of those cases [4,6].

Mandatory bivalent (serogroups A and C) meningococcal vaccination for all pilgrims from 1987 brought the disease under control during the Hajj for more than a decade [6,7]. Switching the vaccination policy to the quadrivalent (serogroups A, C, W, and Y) meningococcal (MenACWY) polysaccharide vaccine in 2002, coupled with chemoprophylaxis at the port of entry for pilgrims arriving from the African meningitis belt, again brought the subsequent epidemics under control [8]. Since then, no further Hajj-related meningococcal outbreaks occurred [6]. The mandatory vaccination policy also applies to residents of Hajj zones and to personnel who serve pilgrims during the Hajj, including healthcare workers (HCWs) (Table 1) [1,9].

Table 1. Current preventive measures mandated by the Saudi Arabian government to control meningococcal disease during Hajj.

<table>
<thead>
<tr>
<th>Measure</th>
<th>When</th>
<th>Age Criteria</th>
<th>Target Group</th>
</tr>
</thead>
</table>
| MenACWY polysaccharide   | Within last 3 years, but ≥10 days before arrival | Any individual > 2 years | a. Visitors to Saudi Arabia for Umra *, Hajj, or seasonal work **  
| vaccine                  |                               |              | b. Residents of Saudi Arabia as follows:  
|                          |                               |              | - Residents of Makkah and Madina at the time of Hajj  
|                          |                               |              | - Residents of all other provinces undertaking the Hajj **  
|                          |                               |              | - Hajj workers ***  
| MenACWY conjugate vaccine| Within last 5 years, but ≥10 days before arrival | Any individual > 2 years | Visitors from African meningitis belt countries for Umra *, Hajj, or seasonal work **  
| Chemoprophylaxis (ciprofloxacin, 1 tablet, 500 mg) | Upon arrival (at port of entry) | Excluding pregnant women |                                                                           |

MenACWY; quadrivalent meningococcal serogroup A, C, Y, and W. * A minor pilgrimage to Makkah outside of the Hajj season. ** Requirements for Hajj and Umra entry visa, and for Hajj permit for domestic pilgrims. *** Including individuals working at points of entry or in direct contact with pilgrims.

Monitoring the annual number of Hajj visas and mandating the vaccine as a prerequisite for the visa application both limited the numbers of overseas pilgrims and improved vaccination rates. For instance, reports on vaccine uptake among overseas pilgrims since 2006 showed a compliance of no less than 96% and reaching up to 100% [10–14]; however, concerns remain among this group of pilgrims, including the receipt of inappropriate vaccines and, due to the limited access to vaccines (including cost), the use of fraudulent vaccination certificates [11,15,16].

Since 2003, Saudi citizens and other expatriate residents in Saudi Arabia who intend to perform Hajj must apply for a Hajj permit with a MenACWY vaccine receipt stipulated as a requirement. Despite this, unauthorized domestic pilgrims often sometimes enter Hajj sites without a permit and...
without formally registering with an official Hajj tour group. Additionally, despite being enforced and freely offered, the vaccine coverage was found to be very low (64%) in 2006 in the only published work reporting vaccine uptake among domestic pilgrims [12]. The rate was also unsatisfactory among domestic HCWs (ranging from 51.7% to 84.7%) in several studies conducted between 2009 and 2018 [17–20]. In recent years, the enforcement of the Hajj permit requirement by rigorous procedures at points of entry into Makkah reduced the number and proportion of domestic pilgrims (from 1.4 million (45%) in 2012 to 600,000 (26%) in 2018) [21]. However, there is no recent study assessing the uptake of meningococcal vaccines among these pilgrims. To this end, a survey was undertaken to evaluate the coverage of MenACWY vaccines among Hajj pilgrims and to identify the key predictors and barriers affecting their uptake, particularly among domestic pilgrims, which was not assessed in previous studies.

2. Materials and Methods

An anonymous cross-sectional survey was distributed among domestic pilgrims present in Mina, a tent city, and a main Hajj site on the outskirts of Makkah, and among overseas pilgrims who were staying in Aziziyah (before moving to tents in Mina), a borough of Makkah, adjacent to Mina, during the Hajj seasons of 2017 and 2018.

2.1. Participant Recruitment

Overseas and official domestic pilgrims were eligible to participate; all other non-pilgrims were excluded. In order to recruit a representative sample of both domestic and international pilgrims, the research team approached domestic pilgrims in their camps in Mina, and overseas pilgrims living in hotels/serviced apartments in Aziziyah. The research team (composed of research doctors and trained volunteer allied health or medical students) randomly approached tour operators to access their tent camps or housing and to invite pilgrims to the study. The research team, after obtaining permission from the tour group leaders, explained the study to their pilgrims, answered any queries they had, and invited them to participate. Participation depended primarily on the cooperation of the tour group leader, and then the pilgrim’s willingness to participate.

No identifiable personal data were collected, and respondents’ completion of the survey was considered implied consent. This study was reviewed and approved by the Institutional Review Board of King Saud University College of Medicine, Riyadh, Saudi Arabia (E-17-2534).

2.2. Survey Design

The survey was designed and reviewed by experts in the field of Hajj and vaccine-preventable diseases. The questionnaire collected data on socio-demographic characteristics (such as age, gender, educational level, and employment status), as well as uptake of meningococcal vaccines as a preparation for Hajj and reasons behind non-receipt of the vaccine in such cases. It also evaluated if this was the participant’s first time to the Hajj, whether the vaccine was freely offered, and the receipt of pre-Hajj health advice. The survey was primarily in English, with Arabic translations available for those who preferred to complete the survey in Arabic. Survey responses were collected using a printed or web-based form securely hosted in Wufoo™ (SurveyMonkey Inc., San Mateo, CA, USA). Written responses were entered into the web-based form, and all data were subsequently exported to a Microsoft Excel™ (Microsoft Corp., Redmond, WA, USA) spreadsheet for analysis.

2.3. Statistical Methods

The proportion of participants responding to each question was reported. To measure the association between predictors and vaccine uptake, odds ratios (OR) with 95% confidence intervals (95% CI) based on the risk estimate statistics were calculated. Pearson’s chi-squared test was used to compare categorical variables and determine associations and correlations. For questions evaluating sources of pre-Hajj health advice and reasons for non-receipt of the vaccine, one sample nonparametric
test (Jeffreys interval) was used to report the proportion of participants providing each response and the 95% CI for the point estimate.

All those who declared previous receipt of the vaccine, regardless of the year of vaccination, were considered as vaccinated; further analysis was done to determine the adherence to the vaccine policy time window. Participants who were unsure about their vaccination history were excluded from the analysis in the OR calculation. A \( p \)-value \( \leq 0.05 \) was considered statistically significant. The statistical analysis was performed using the Statistical Package for Social Sciences (SPSS\textsuperscript{TM}) for Windows\textsuperscript{TM} v.25.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Participant Characteristics

In total, 513 pilgrims agreed to participate in the study, of whom 509 completed the survey; the remaining four submitted blank forms and, hence, were excluded from the denominator. Only 444 respondents declared their age, ranging from 13 to 82 years (mean 36, SD \( \pm \)12.6). Males comprised 86% of the sample, and local pilgrims accounted for 85%. Table 2 summarizes the demographic characteristics of the surveyed participants.

3.2. Meningococcal Vaccine Uptake

Of the 476 participants who declared their vaccination status, only 389 (81.7%) confirmed receipt of a meningococcal vaccine; 64 (13.4%), all domestic pilgrims, did not receive the vaccine, and 23 (4.8%) were unsure about their vaccination status. Almost all (93.5% (58/62)) overseas pilgrims declared receipt of the vaccine, although four (6.5%) were unsure, compared with 80.9% (321/397) of domestic pilgrims who received the vaccine (\( p < 0.01 \)), 61/397 (15.3%) who did not, and 15/397 (3.8%) who were unsure (Table 3). Employed participants were twice as likely to be vaccinated as those who were not employed, and those who received pre-Hajj health advice from any source, and those with a tertiary qualification had a higher vaccination uptake rate. Among domestic pilgrims, those from Makkah province were almost three times more likely to miss out on the vaccine compared to those from other provinces.
Hajj pilgrims were more likely to receive advice from professional sources than domestic pilgrims (16%; OR = 9.6, 95% CI = 5.3–17.3, p < 0.001). Notably, overseas pilgrims (64%) were more likely to receive advice from professional sources, including general practitioners or a specialized travel clinic; 61% (309/504) received advice from “professional” sources, and 19% (97/504) did not receive any advice. Only 19.4% (98/504) of participants received pre-Hajj health advice from one or more sources, and 70.6% (356/504) received advice from “non-professional” sources.

Table 2. Demographic characteristics of the domestic and overseas pilgrims.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All n/N * (%)</th>
<th>Domestic Pilgrims n/N * (%)</th>
<th>Overseas Pilgrims n/N * (%)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>509*</td>
<td>416/489 (85.1)</td>
<td>73/489 (14.9)</td>
<td></td>
</tr>
<tr>
<td>Age in years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>36 (± 12.6)</td>
<td>34.7 (± 12)</td>
<td>42 (± 13.4)</td>
<td>&lt; 0.001 ***</td>
</tr>
<tr>
<td>Range (Median)</td>
<td>13–82 (33.8)</td>
<td>13–82 (32.6)</td>
<td>21–69 (38.9)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male:female</td>
<td>6:1</td>
<td>7.5:1</td>
<td>3:1</td>
<td>0.03 ***</td>
</tr>
<tr>
<td>Country of residence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>398/499 (79.8)</td>
<td>398/412 (96.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pakistan</td>
<td>33/499 (6.6)</td>
<td>0</td>
<td>0/73 (41.1)</td>
<td></td>
</tr>
<tr>
<td>South Africa</td>
<td>28/499 (5.6)</td>
<td>0</td>
<td>28/73 (38.4)</td>
<td></td>
</tr>
<tr>
<td>Egypt</td>
<td>11/499 (2.2)</td>
<td>7/412 (1.7)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Malawi</td>
<td>6/499 (1.2)</td>
<td>0</td>
<td>6/73 (8.2)</td>
<td></td>
</tr>
<tr>
<td>Zambia</td>
<td>5/499 (1)</td>
<td>0</td>
<td>5/73 (6.8)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>18/499 (3.6)</td>
<td>7/412 (1.7)</td>
<td>4/73 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Highest qualification</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No formal education</td>
<td>4/499 (0.8)</td>
<td>2/411 (0.5)</td>
<td>1/70 (1.4)</td>
<td></td>
</tr>
<tr>
<td>School certificate †</td>
<td>43/499 (8.6)</td>
<td>34/411 (8.2)</td>
<td>4/70 (5.7)</td>
<td></td>
</tr>
<tr>
<td>High school certificate §</td>
<td>124/499 (24.8)</td>
<td>100/411 (24.3)</td>
<td>21/70 (30)</td>
<td></td>
</tr>
<tr>
<td>Diploma</td>
<td>58/499 (11.6)</td>
<td>39/411 (9.5)</td>
<td>12/70 (17.1)</td>
<td></td>
</tr>
<tr>
<td>University undergraduate degree</td>
<td>215/499 (43.1)</td>
<td>184/411 (44.8)</td>
<td>30/70 (42.9)</td>
<td></td>
</tr>
<tr>
<td>University postgraduate degree</td>
<td>55/499 (11)</td>
<td>52/411 (12.7)</td>
<td>2/70 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>168/501 (33.5)</td>
<td>134/412 (32.5)</td>
<td>25/69 (36.2)</td>
<td>0.61</td>
</tr>
<tr>
<td>Yes</td>
<td>333/501 (66.5)</td>
<td>278/412 (67.5)</td>
<td>44/69 (63.8)</td>
<td></td>
</tr>
<tr>
<td>Hajj attendance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First time</td>
<td>285/500 (57)</td>
<td>212/409 (51.8)</td>
<td>60/71 (84.5)</td>
<td>&lt; 0.001 ***</td>
</tr>
<tr>
<td>&gt; 1 time previously</td>
<td>215/500 (43)</td>
<td>197/409 (48.2)</td>
<td>11/71 (15.5)</td>
<td></td>
</tr>
</tbody>
</table>

SD—standard deviation. * The total number of respondents with complete information for each individual variable. ** Twenty participants with unknown allocation status (overseas or domestic). *** Statistically significant. † Holders of any visa other than a Hajj visa were officially treated as domestic pilgrims. ‡ Year 10 equivalent; § year 12 equivalent.
Table 3. Meningococcal vaccine uptake.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall Meningococcal Vaccine Uptake</th>
<th>Meningococcal Vaccine Uptake among Domestic Pilgrims</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N * (%)</td>
<td>OR ** (95% CI)</td>
</tr>
<tr>
<td>All</td>
<td>389/476 (81.7)</td>
<td>321/397 (80.9)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>322/380 (84.7)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Female</td>
<td>53/58 (91.4)</td>
<td>1.9 (0.7–4.98)</td>
</tr>
<tr>
<td>Origin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Domestic</td>
<td>321/382 (84)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Overseas</td>
<td>58/58 (100)</td>
<td>n.a</td>
</tr>
<tr>
<td>Hajj attendance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First time</td>
<td>208/246 (84.6)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>≥ 1 time previously</td>
<td>174/199 (87.4)</td>
<td>1.3 (0.7–2.2)</td>
</tr>
<tr>
<td>Tertiary qualification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>122/150 (81.3)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Yes</td>
<td>262/297 (88.2)</td>
<td>1.7 (1.0–2.5)</td>
</tr>
<tr>
<td>Employed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>113/144 (78.5)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Yes</td>
<td>269/302 (89.1)</td>
<td>2.2 (1.3–3.8)</td>
</tr>
<tr>
<td>Received pre-Hajj health advice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>64/89 (71.9)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Yes</td>
<td>322/360 (89.4)</td>
<td>3.3 (1.9–5.9)</td>
</tr>
</tbody>
</table>

OR, odds ratio; 95% CI, 95% confidence interval; p, p-value; ref, reference value; n.a, not available. * Total number of respondents with vaccination status (excluding “unsure” respondents) and complete information for each individual variable. ** For OR calculation, responses with “unsure” for vaccination status were excluded. ¶ Includes all participants with vaccination status. § Statistically significant.
3.3. Participant Adherence to Vaccination Policy

Overall, among the 389 vaccinated individuals, 329 (84.6%) received the vaccine within the last three years, 12 (3.1%) received it over three years prior to Hajj attendance, and 48 (11.9%) did not declare the year of vaccination. Thus, 20.5% (70/341) of domestic pilgrims failed to confirm their adherence to the complete vaccination policy (either did not receive the vaccine at all, received it over three years prior, or were unsure about their vaccination status). This translates to an almost seven-fold increased risk of non-compliance with the vaccine policy compared to overseas pilgrims (OR = 6.8, 95% CI = 1.6–28.8), \( p < 0.01 \). Lack of awareness that the vaccine is a mandatory requirement (63.2%, 36/57) was the main reason given for not receiving the vaccine (Figure 1).

![Figure 1](image.png)

**Figure 1.** Reasons for non-receipt of meningococcal vaccine among unvaccinated domestic pilgrims: proportion of participants providing each reason with the 95% confidence interval for the point estimate.

3.4. Vaccination Venues

Domestic pilgrims were mainly vaccinated at primary health care centers (79.3%), while overseas pilgrims mostly visited hospitals or travel clinics (70.3%).

3.5. Cost of Vaccination

Overall, 55 (15.1%) participants paid for the vaccine. Overseas pilgrims, women, and those who attended Hajj for the first time were significantly more likely to pay for the vaccine than domestic pilgrims, men, or those who attended Hajj previously (Table 4).

3.6. Receipt of Pre-Hajj Advice

Only 19.4% (98/504) of participants received pre-Hajj health advice from one or more “professional” sources, including general practitioners or a specialized travel clinic; 61% (309/504) received advice from “non-professional” sources, and 19% (97/504) did not receive any advice (Figure 2). Notably, overseas pilgrims (64%) were more likely to receive advice from professional sources than domestic pilgrims (16%; OR = 9.6, 95% CI = 5.3–17.3, \( p < 0.001 \)).
Table 4. Covering the cost of vaccination.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Proportion of Participants Who Paid for the Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N * (%)</td>
</tr>
<tr>
<td>All</td>
<td></td>
</tr>
<tr>
<td>All participants³</td>
<td>55/364 (15.1)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>38/302 (12.6)</td>
</tr>
<tr>
<td>Female</td>
<td>16/49 (32.7)</td>
</tr>
<tr>
<td>Origin</td>
<td></td>
</tr>
<tr>
<td>Domestic</td>
<td>30/307 (9.8)</td>
</tr>
<tr>
<td>Overseas</td>
<td>23/48 (47.9)</td>
</tr>
<tr>
<td>Pakistan</td>
<td>17/17 (100)</td>
</tr>
<tr>
<td>South Africa</td>
<td>3/20 (15)</td>
</tr>
<tr>
<td>Other</td>
<td>9/27 (33.3)</td>
</tr>
<tr>
<td>Hajj attendance</td>
<td></td>
</tr>
<tr>
<td>≥ 1 time previously</td>
<td>13/165 (7.9)</td>
</tr>
<tr>
<td>First time</td>
<td>41/193 (21.2)</td>
</tr>
<tr>
<td>Tertiary qualification</td>
<td></td>
</tr>
<tr>
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<td>31/246 (12.6)</td>
</tr>
<tr>
<td>No</td>
<td>22/112 (19.6)</td>
</tr>
<tr>
<td>Employed</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>32/246 (13)</td>
</tr>
<tr>
<td>No</td>
<td>21/108 (19.4)</td>
</tr>
</tbody>
</table>

OR, odds ratio; 95% CI, 95% confidence interval; p, p-value; ref, reference value. * Total number of respondents with known source of payment and complete information for each individual variable. § Includes all participants with known source of payment. § Statistically significant.

Figure 2. Sources of pre-Hajj health advice among participants who received such advice: proportion of participants providing each response with the 95% confidence interval for the point estimate.

4. Discussion

The key finding of this study is that around one-sixth of domestic Hajj pilgrims failed to receive the compulsory MenACWY vaccine in recent years. Meningococcal vaccination is a visa prerequisite for international pilgrims; thus, a high coverage among overseas pilgrims was expected and demonstrated (93.5%). In this regard, the findings of this study are consistent with previous reports. Compliance among overseas pilgrims ranged from 96% to 98% between 2006 and 2010 [13], and two recent studies conducted at King Abdul Aziz International Airport, among 796 and 5235 arriving overseas pilgrims in 2013 and 2014, revealed uptake rates of 98.2% and 100%, respectively [10,11]. However, assessing
compliance to other measures of the vaccination policy among overseas pilgrims, such as type and timing of vaccination, is recommended [11,16].

Nevertheless, it is concerning that, despite regulatory efforts, vaccine uptake among local pilgrims who form nearly one-third of total attendees at Hajj each year is unacceptably low. Although the vaccine uptake identified in this survey (85%) is higher than that reported by El Bashir et al. during the Hajj in 2006 (64%) among domestic pilgrims who attended the National Guard Clinics in Makkah [12], it appears that the official regulation that mandates meningococcal vaccination as a prerequisite for a Hajj permit for locals is less effective than that applied to international pilgrims, and a significant number of domestic pilgrims are able to avoid vaccination. Ensuring no Hajj permit is granted unless a valid certificate is provided may improve the situation; however, it is possible that there are more prevailing factors involved, including education of the general population, as well as HCWs.

Several studies demonstrated suboptimal meningococcal vaccine coverage among local HCWs, which, at best, did not exceed 85% among highly vulnerable hospital emergency room HCWs in Madina in 2015 [19]. A similar rate (82.4%) was also reported among HCWs working in Mina and Arafat, principal Hajj zones in Makkah, in 2003 [17]. Other studies found uptake rates as low as 67.1% and 76.1% among HCWs serving pilgrims in 2009 and 2018, respectively [18,20].

Longer distance of travel appears to act as a motivator for overseas pilgrims to better prepare for Hajj and to seek and follow health advice. This was also noted even among domestic participants in this survey. Similarly, in a previous vaccine uptake survey among domestic pilgrims, fewer pilgrims (50%) from Hajj zones (Makkah and Jeddah) were shown to be vaccinated against MenACWY than pilgrims from other regions in Saudi Arabia (71%) [12]. Moreover, pilgrims from Makkah city were found to have lower vaccination coverage against seasonal influenza than pilgrims from the rest of the country (adjusted OR = 0.52, 95% CI = 0.37–0.72, \( p < 0.001 \)) [22].

An important finding of this survey is that receiving pre-travel health advice, regardless of the source, substantially increased compliance with the vaccination policy. The majority of overseas pilgrims received “professional” pre-Hajj health advice, while locals tended to rely on “social” sources. However, receiving any pre-travel health advice, being employed, and having a tertiary qualification were each individually associated with greater compliance with the vaccination policy. Previous reports on uptake of other recommended vaccines at Hajj also indicated that receiving pre-travel health advice was a considerable motivator for receiving vaccinations against other diseases [14,23]. Furthermore, in a large survey among residents of Gulf Cooperation Council countries, doctors’ advice was the leading motivator for receipt of influenza vaccine [24]. Worksite immunization was shown to be effective in facilitating influenza vaccine uptake in Saudi Arabia [25]. Similarly, some employed participants of this survey indicated receiving the meningococcal vaccine at or through their workplace. This may explain the higher vaccine uptake among employed participants compared with those who identified themselves as unemployed. Additionally, more educated pilgrims were more likely to receive the meningococcal vaccine than those with lower educational attainment. A cross-sectional study of Australian Hajj pilgrims also demonstrated that having a university education was associated with a higher likelihood of receiving recommended Hajj vaccines (OR = 3.4, 95% CI = 1.7–6.7, \( p = 0.01 \)) [14]. Previous reports also described a higher rate of vaccine uptake in women preparing to be pilgrims [20,26,27]. The association observed in this survey was in the same direction, but the difference with men was not statistically significant, which may be due to the low proportion of women who participated in the survey.

Unvaccinated domestic pilgrims named several barriers to vaccination; lack of awareness that the vaccine is compulsory was the most commonly cited reason, followed by lack of time. Lack of awareness as a barrier to vaccination is consistent with previous findings on meningococcal vaccine uptake during Hajj among local HCWs [19,20]. In fact, lack of knowledge was also highlighted in previous studies reporting uptake of other Hajj recommended vaccines such as influenza vaccine, for both Saudi [22] and international pilgrims (during the influenza A (H1N1) pandemic) [28]. Lack of awareness was also the main reason reported by Australian pilgrims in 2014 for not receiving
Hajj recommended vaccines [14]. Lack of time was also found to be a barrier to vaccination among emergency room HCWs in Madina [19] and was shown to be a more significant barrier to influenza vaccination among domestic male pilgrims compared to female pilgrims [22].

Surprisingly, a substantial minority of domestic pilgrims also reported having to pay for their vaccine, which in principle should be provided freely in major public primary healthcare facilities across the country. Unfortunately, the wording of the pre-defined questionnaire had limited ability to identify this as a barrier among domestic pilgrims.

New, highly immunogenic, conjugate vaccines are replacing the older polysaccharide vaccines in many developed countries, and they are increasingly being recommended for Hajj pilgrims. Conjugate vaccines are more effective in controlling the carriage of meningococci [29,30] but are considerably more expensive. Meningococcal serogroups that are not covered by the current quadrivalent vaccine were frequently isolated from throat swabs collected from pilgrims, namely, serogroups B and, less frequently, X [31–33]. A recent systematic review concluded that serogroup B dominated the carriage acquisition among Hajj pilgrims [32], and most carriers received the polysaccharide vaccine, which is not expected to reduce the carriage acquisition of serogroups contained in the vaccine [34,35]. The opportunity to prevent future outbreaks depends on an ongoing review of the current mandatory vaccination policy in view of these and future developments.

Promisingly, most of the participants received some pre-Hajj health advice, but the fact that 84% of vaccinated domestic pilgrims (who certainly had a pre-Hajj contact with health professionals) stated non-receipt of advice from a “professional” source deserves careful attention. This provides an important reminder to local health authorities to take advantage of the national Hajj immunization program as an opportunity for providing face-to-face pre-Hajj health education.

The strength of this survey is that it provides a snapshot regarding the current situation with uptake of the compulsory meningococcal vaccine among mainly domestic Hajj pilgrims, and, for the first time, it provides insight into some of the barriers to vaccination. However, since pilgrims are often too busy to complete forms, the small sample size and the submission of incomplete responses are key limitations of this survey. Additionally, the small number of unvaccinated participants limits the ability to draw reliable conclusions regarding the true role of specific barriers. Furthermore, the data are self-reported, and we had no way of validating vaccination histories; moreover, the questionnaire did not differentiate between conjugate and polysaccharide meningococcal vaccines. Finally, we considered all those who stated previous receipt of the vaccine as vaccinated; however, since some respondents did not state the year of vaccination, the true uptake rates may be lower than reported here. The inability to include “unauthorized” domestic pilgrims also adds to the potential overestimation of the true vaccine uptake rate among domestic pilgrims.

In conclusion, this survey demonstrates that many domestic pilgrims miss the compulsory meningococcal vaccine prior to attending Hajj. Overseas pilgrims appear to have good uptake of the vaccine, as expected from the mandatory vaccination for visa policy. Receipt of pre-travel health advice, regardless of the source, is a key motivator for vaccine uptake, and lack of awareness about the vaccination policy is an important barrier. Improving vaccine uptake likely requires system-wide strategies, such as reducing financial barriers and increasing the availability of vaccination centers, as well as greater education of the public, particularly targeting those who are intending to perform Hajj, regarding Hajj-related health risks and prevention strategies. Strategies to improve the ability of local HCW to proactively provide preventive pre-Hajj health advice are also needed. Additionally, the success of the mandatory vaccination policy that is applied to international pilgrims should be modeled to improve compliance with the domestic policy through more rigorous checks and measures. Ongoing evaluation of such strategies is required to monitor the true uptake of vaccines and other health-promoting behaviors among domestic (and international) pilgrims, so that appropriate public health responses can be made to evolving situations.


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**Conflicts of Interest:** Professor Robert Booy receives funding from Baxter, CSL/Seqirus, GSK, Merck, Novartis, Pfizer, Roche, Romark, and Sanofi Pasteur for the conduct of sponsored research, travel to present at conferences, or consultancy work; all funding received is directed to research accounts at The Children’s Hospital at Westmead. Dr Harunor Rashid receives fees from Pfizer, Novartis, and Sanofi Pasteur for consulting or serving on an advisory board. The other authors have no conflicts of interest to declare in relation to this manuscript.

**References**


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3.2 Meningococcal vaccine uptake among health care workers in Hajj


What is the context?

- Meningococcal vaccination is mandatory for health care workers serving Hajj pilgrims.
- Previous reports have suggested suboptimal coverage among health care workers.
- Evidence on facilitators or barriers to vaccination are limited.

What is new?

- A cross-sectional survey targeting exclusively domestic health care workers and trainees who serve pilgrims during Hajj, aiming to identify vaccine coverage, and its facilitators and barriers.

What is the impact?

- There is a need for certain measures to increase awareness of and facilitate access to meningococcal vaccines in order to improve acceptance and uptake.
Mandatory meningococcal vaccine, and other recommended immunisations: Uptake, barriers, and facilitators among health care workers and trainees at Hajj

Al-Mamoon Badahdah, Mohammad Alfelali, Amani S Alqahtani, Saeed Alsharif, Osamah Barasheed, Harunor Rashid; the Hajj Research Team
workforce, and to explore the facilitators and barriers for their uptake. Key findings of this study are: some HCWs in Hajj, mostly males, failed to receive these vaccines, including the compulsory meningococcal vaccine. Health authority’s recommendation was the main motivator. Lack of awareness about vaccines and the respondents’ perception that they were up-to-date with all vaccinations; were the two main barriers.


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DOI: https://dx.doi.org/10.12998/wjcc.v6.i16.1128

INTRODUCTION

Hajj is the largest annual mass gathering event that takes place in designated areas in Makkah, Saudi Arabia where two to three million people assemble from all corners of the world on specific dates of the last month of the lunar calendar. Establishing a healthy environment during Hajj is one of the strategic objectives of the host country[1,2]. Intense congestion during Hajj along with compromised hygiene, shared accommodation and air pollution amplify the risk of meningococcal and other air-borne diseases including influenza and pneumonia[3].

In the last few decades, meningococcal outbreaks from Hajj gathering have been a major global public health concern[4,6]. Two major intercontinental outbreaks of meningococcal disease occurred during Hajj seasons of 1987 (caused by serogroup A) and again during 2000-01 seasons (caused by serogroup W) affected thousands of individuals globally[6,9]. Currently, it is compulsory for anyone, including health care workers (HCWs) who are going to attend congregation, serve pilgrims or reside in Hajj zones whether as pilgrims or seasonal workers to be vaccinated with a quadrivalent meningococcal vaccine (against serogroups A, C, W and Y)[3].

Lately seasonal influenza and pneumonia have been major morbidities among Hajj pilgrims[10,12]. More than 90% of pilgrims develop at least one respiratory symptom while at Hajj[13]. Respiratory viruses, especially influenza, are the most common causes of acute respiratory infections among pilgrims[10,14,16]. The attack rate of influenza among pilgrims ranges from 4% to 15%[17,18]. Currently, influenza vaccination is strongly recommended for Hajj pilgrims and their carers, especially for individuals at higher risk of severe influenza[19].

Pneumonia is a leading cause of hospitalisation, admission to intensive care units, and severe sepsis and septic shock during Hajj[12,20-21]. The point prevalence of pneumonia has risen substantially during Hajj, as it reached up to 340/100000 pilgrims among Iranian in
2005 compared to 4.8/100000 reported in 1986\(^{23-25}\). Studies revealed an increase of the pneumococcal nasal carriage up to 2.7-fold before and after Hajj\(^{26,27}\). The Saudi Thoracic Society and independent experts also recommend pneumococcal vaccines especially for those at higher risk of complications\(^{28,29}\).

An estimated 70000 emergency room visits and 12000 hospitalisations occur during a typical Hajj season, and a physician needs to see over 600 patients and a nurse looks after about 400 patients per day during Hajj\(^{30}\). To cater for such a large number of pilgrims each year about 30000 HCWs are mobilised from across Saudi Arabia to the Hajj sites in Makkah and Madinah; also, many trainee medics willfully volunteer at Hajj.

Unvaccinated personnel who have contact with patients put themselves, their colleagues and patients at risk of preventable diseases. Coexistence of Hajj setting as well as excessive workload environment may double these risks. For instance, Al-Asmary et al\(^{31}\) found that a quarter of HCW in Hajj medical admission developed acute respiratory infections, contact with pilgrims was a significant risk factor for acquisition of this infection. Thus, ensuring vaccination of HCWs at Hajj is very important to protect themselves and their patients. These include mandatory meningococcal vaccine, and highly recommended influenza vaccine; both are funded for HCWs who care for Hajj pilgrims. Yet, the uptake of these vaccines among HCWs at Hajj has been suboptimal\(^{31-35}\), there is no data on pneumococcal vaccine uptake among HCWs at Hajj. In previous reports non-availability of vaccine and lack of time were key barriers to vaccination among HCWs at Hajj\(^{28,30}\), however the latest data are not known, and no data on facilitators of vaccination.

To this end, we have conducted a survey to evaluate the uptake of meningococcal, influenza and pneumococcal vaccines among HCWs at Hajj, and explored the key factors that affected vaccine uptake including facilitators of vaccination.

### MATERIALS AND METHODS

An anonymous cross-sectional online survey was conducted among HCWs and trainees who were employed in Saudi Arabia and worked or volunteered during the Hajj 2015-2017. The survey was distributed among HCWs, including trainees and students who volunteered at Hajj, through their line managers, or by visiting their hospitals and healthcare centres in Makkah and Mina, a major Hajj spot at the outskirts of Makkah. The survey link was sent to the potential participants via short message service, WhatsApp Messenger or email. Overseas HCWs who accompanied the pilgrims or those who work in foreign Hajj medical missions were excluded. Following invitation, the potential respondents acknowledged their acceptance to participate electronically before starting to fill the e-form. The questionnaire included questions about their demographics such as age, gender, current employment, presence or absence of chronic medical conditions, including diabetes, bronchial asthma, other lung or heart diseases, and malignancies. Any participant reporting at least one of these underlying medical conditions and/or aged ≥ 65 years was considered “at increased risk”. The questionnaire then asked if the HCWs received meningococcal, influenza and pneumococcal vaccines as a part of their preparation for secondment at Hajj. It also asked about the reasons for receipt or non- receipt of vaccines. Data analysis was performed using the Statistical Package for Social Sciences (SPSS) v.25.0 (SPSS, Inc., Chicago, IL, United States). Pearson’s \(\chi^2\) test was used to compare categorical variables and “risk estimate” statistics was used to calculate odds ratio (OR). A two-tailed \(P\)-value < 0.05 was considered statistically significant.

This study was reviewed and approved by Institutional Review Board of King Abdullah Medical City, Saudi Arabia (Ref: 15-202). Respondents’ completion of the survey was considered as their implied consent, so signed informed consent was not obtained, and no identifiable personal data were collected.

### RESULTS

A total of 138 respondents participated in the survey. Among participants who declared their age (3 did not declare age) the age ranged from 20 to 59 (median 25.6) years with a male to female ratio of 2:5:1. Students/trainee HCWs formed the largest group (41%) followed by nurses (28%) and physicians (16%). Eight per cent \((n = 11)\) respondents were “at increased risk” either because of age or having a pre-existing medical condition. Sixty six per cent (91/138) of the respondents attended Hajj at least once in the past (Table 1).

Of all respondents, 11.6% (16/138) reported receiving all three (meningococcal, influenza, pneumococcal) vaccines, 15.2% (21/138) did not receive any of the vaccines, another 2.9% (4/138) were unsure of their vaccination status. Females were more likely to receive a vaccine than males \([OR 3.6, 95% confidence interval (95%CI): (1.0-12.7), P < 0.05]\).

As for meningococcal vaccine, 76.1% (105/138) reported receiving it, 21.7% (30/138) did not receive, and 2.2% (3/138) were unsure (Table 1). Of those who attended Hajj for the first time, 27.7% (13/47) reported not receiving meningococcal vaccine that means 9.4% (13/138) of the whole sample never received this vaccine at all. Sixty two per cent (86/138) received both meningococcal and influenza vaccines. Vaccination against meningococcal disease was significantly higher in females than males \([OR 3.8, 95%CI: 1.2-11.6, P = 0.01]\). Sixty eight per cent (94/138) reported receiving influenza vaccine, 29% (40/138) did not and 3% (4/138) were unsure. Again, vaccination rate was significantly higher in females than males \([OR 2.9, 95%CI: 1.1-7.1, P = 0.02]\). Only 13.8% (19/138) declared receiving the pneumococcal vaccine as preparation for their Hajj duty, 75.4% (104/138) not
received, and 10.9% (15/138) were unsure. No gender difference was observed in the uptake of pneumococcal vaccine.

The reasons for receipt and non-receipt of vaccines are listed in Figures 1 and 2 respectively, willingness to follow health authority’s recommendation was the main reason for receipt of vaccine (78.8%) while believing that they were up-to-date with vaccination and hence did not need any more vaccines (39.8%), and unawareness of Hajj vaccines (31.9%) were the prime reasons for non-receipt.

**DISCUSSION**

This survey aimed to assess the uptake of the three (meningococcal, influenza, pneumococcal) vaccines among HCWs, a key working group during Hajj, and to explore the important barriers and facilitators. The key findings of this study are that some HCWs at Hajj, mostly males, failed to receive the key Hajj vaccines including the compulsory meningococcal vaccine. Health authority’s recommendation was the main motivator. Lack of awareness about vaccines and a false perception that the respondents were up-to-date with all vaccinations were the two single most important barriers.

Despite the historical importance of meningococcal disease and mandatory requirement of vaccination against it for attending Hajj, at least 9% HCWs and trainees failed to receive the freely available compulsory meningococcal vaccine. In fact, such a poor vaccine uptake was reported in surveys conducted among HCWs in 2003, 2009 and 2014 with the respective uptake of 82.4%, 67.1% and 69.1% [32,33,35]. Non vaccination against a fatal disease among HCWs, who often provide intensive medical care to ill pilgrims, is a grave concern.

Meningococcal vaccination is a visa requirement for international pilgrims, so the vaccine coverage is essentially 100% [36,37], however domestic pilgrims and

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**Table 1** Characteristics of the participants and their vaccine uptakes n (%)  

<table>
<thead>
<tr>
<th>No. of participants</th>
<th>Meningococcal vaccine</th>
<th>Influenza vaccine</th>
<th>Pneumococcal vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Uptake  OR (95%CI)</td>
<td>Uptake  OR (95%CI)</td>
<td>Uptake  OR (95%CI)</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Participants</td>
<td>138 (100)</td>
<td>94 (68.1)</td>
<td>19 (13.8)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>98 (71)</td>
<td>61 (62.2)</td>
<td>14 (14.3)</td>
</tr>
<tr>
<td>Female</td>
<td>40 (29)</td>
<td>33 (82.5)</td>
<td>5 (12.5)</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Students</td>
<td>57 (41.3)</td>
<td>36 (63.2)</td>
<td>7 (12.3)</td>
</tr>
<tr>
<td>Non-student</td>
<td>81 (58.7)</td>
<td>58 (71.6)</td>
<td>12 (14.8)</td>
</tr>
<tr>
<td>Associated HCW</td>
<td>15 (10.8)</td>
<td>8 (53.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nurse</td>
<td>39 (28.3)</td>
<td>28 (71.8)</td>
<td>7 (17.9)</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>5 (3.6)</td>
<td>5 (100)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Physician</td>
<td>22 (15.9)</td>
<td>17 (77.3)</td>
<td>4 (18.2)</td>
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<td>Hajj attendance</td>
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<tr>
<td>First time</td>
<td>47 (34.1)</td>
<td>34 (72.3)</td>
<td>9 (19.1)</td>
</tr>
<tr>
<td>Not first time</td>
<td>91 (65.9)</td>
<td>60 (65.9)</td>
<td>10 (11)</td>
</tr>
<tr>
<td>2 to 5 times</td>
<td>65 (47.1)</td>
<td>49 (75.4)</td>
<td>8 (12.8)</td>
</tr>
<tr>
<td>&gt; 5 times</td>
<td>26 (18.8)</td>
<td>22 (84.6)</td>
<td>2 (7.7)</td>
</tr>
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<td>Risk group</td>
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<td></td>
</tr>
<tr>
<td>Not at risk</td>
<td>125 (91.9)</td>
<td>83 (66.4)</td>
<td>16 (12.8)</td>
</tr>
<tr>
<td>At risk</td>
<td>11 (8.1)</td>
<td>9 (81.8)</td>
<td>3 (27.3)</td>
</tr>
</tbody>
</table>

For calculating OR, those who were “unsure” about their vaccination status were considered unvaccinated. Statistically significant. OR: Odds ratio; 95%CI: 95% confidence interval; ref: Reference value.

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**Figure 1** Reasons for receipt of vaccines.
HCWs evade such requirement leading to suboptimal vaccination rate as low as 64% among domestic pilgrims compared to 100% vaccination rate among UK pilgrims[27]. However, achieving optimum vaccination by the appropriate vaccine is still challenge even among the overseas pilgrims. For instance, a minority of Nigerian pilgrims were found to be vaccinated with the monovalent meningococcal serogroup A vaccine whereas the policy was to use the quadrivalent A/CWY vaccine[30]. Occasional use of fake vaccination certificate was another challenge in some countries[39].

Influenza vaccination of HCWs during Hajj is highly recommended[19], yet 29% participants in this study reported not receiving it before attending Hajj. Four previous studies evaluated the coverage of influenza vaccination among HCWs in Hajj with the uptake ranged from as low as 5.9% in 2003, to 61.6% in 2005, 50.9% in 2009 and 52.7% in 2013-15[31-33,40]. Even the uptake of the 2009 influenza A (H1N1) pandemic vaccine remained between 22% and 47%[13,34].

The uptake rate in non-Hajj setting is almost similar, ranging from 21% to 51% in several surveys conducted between 2003 and 2014[34-45], and among Saudi medical students it reached 57.2% in 2017[46]. Furthermore, a strong vaccine hesitancy was revealed in a recent study where 13% of HCWs reported not taking influenza vaccine in the past, and would not receive it in the future[47].

Although recent increase in influenza vaccination rate is promising, the suboptimal uptake in this important occupational group, who are expected to be vaccinated even when not serving at Hajj, is a concern. Recently, Saudi Arabian Ministry of Health (MoH) have made the Basic Infection Control Skills License (BICSL), mandatory for all HCWs. BICSL licensure includes, among others, receiving meningococcal and influenza vaccines and the measure is expected to enhance the coverage of both vaccines among HCWs.

The lower uptake rate of meningococcal and influenza vaccines among males could be due to their lower preventative sense, notably towards preemptive and pre-travel advices, or could be a chance finding seeing that most of the survey participants were male[48]. A Dutch study involving Hajj pilgrims showed that being a female was an independent predictor for accepting dTP vaccine[49].

Although no official recommendation for routine pneumococcal vaccination for HCWs exists, experts have recommended it for Hajj attendees considered to be “at increased risk”[28,29]. Our findings showed suboptimal vaccination rate (13.8%) even among “at increased risk” group (27.3%). Previously, a much lower vaccination rate (1.5%) was reported among “at increased risk” international pilgrims, however, much higher uptake (29%-48%) among “at increased risk” pilgrims from developed countries is reported[50].

Promisingly, the main reason for receipt of vaccines was to follow the health authority’s recommendation but there were several key misperceptions. A false belief among HCWs that they were up-to-date with their vaccinations and that they did not need any more vaccines for Hajj attendance was a key barrier. This belief may have stemmed from their lack of awareness about the requirement and the availability of Hajj vaccines, and their presumption that just for joining the congregation they may not need the vaccinations since they were local residents. HCWs’ reliance on other preventive measures and their claimed ability to know how to ward off an infection without vaccination were other important barriers. Some of these barriers were previously reported among HCWs serving at Hajj[34,35]. Workplace vaccination campaigns could make a difference and was found to be successful in Saudi Arabia. For instance, assigning a dedicated nurse in each department to conduct vaccinations during an annual in-hospital campaign increased staff influenza vaccination up to three folds at a tertiary hospital in Saudi Arabia (from 29% to 77%, 81% and 67%)[45].

The strength of this survey is that it gives a very quick snapshot about Hajj HCWs’ uptake of three vaccines: a mandatory vaccine (meningococcal), a highly desirable vaccine (influenza), and an optional vaccine (pneumococcal), and for the first time provides insight on motivators of vaccination. However, this study is fraught with limitations. Small sample size is a key limitation of this survey, HCWs are too busy to complete a survey form, hence like most other surveys involving HCWs at Hajj it has a small sample size. Also, the data are self-reported, and we had no way to validate their vaccination histories but since HCWs are expected...
to have sufficient health literacy the information are considered to be reliable. The survey did not distinguish between polysaccharide and conjugate meningococcal vaccines, and both vaccines were used in Saudi Arabia during the survey period. Furthermore, the questionnaire did not distinguish those who received the meningococcal vaccine in the previous years versus the current year. Finally, since the survey was online and because we wanted to make it simple for the busy HCWs, we did not ask about reasons for receipt or non-receipt of individual vaccines, so the responses received could be meant for any one or all the three vaccines.

In conclusion, this survey shows that many HCWs at Hajj miss out the compulsory and highly recommended vaccines; lack of awareness is a key barrier and authority’s advice is an important motivator. Health education followed by stringent measures may be required to improve their vaccination rate. Evaluation of the role of on-going measures such as workplace vaccination campaigns and the BICSL is needed to better understand the uptake of vaccination among HCWs at Hajj.

ARTICLE HIGHLIGHTS

Research background
In the last few decades, meningococcal outbreaks from Hajj gathering have been a major global public health concern. It is now compulsory for anyone who is going to attend Hajj congregation or serve the pilgrims to be vaccinated with a quadrivalent meningococcal vaccine (against serogroups A, C, W and Y). Seasonal influenza vaccine is also highly advised for all Hajj attendees, and pneumococcal vaccine is recommended for pilgrims with co-morbidities.

Research motivation
The uptake of these vaccines among health care workers (HCWs) at Hajj has been suboptimal and there is no data on pneumococcal vaccine uptake. In previous reports non-availability of vaccine and lack of time were key barriers to vaccination among HCWs at Hajj, however there is no data on facilitators of vaccination.

Research objectives
The objectives are to evaluate the uptake of meningococcal, influenza, pneumococcal vaccines among HCWs who serve at Hajj, and to explore the key factors, including facilitators, affecting their vaccination rate.

Research methods
An anonymous cross-sectional online survey was conducted among HCWs at Hajj. For HCWs who serve at Hajj, the Middle East and North Africa (MENA) region is the most likely destination, followed by Asia and then Africa. The questionnaire consists of 31 questions that are grouped into five sections: demographics, meningococcal vaccine; influenza vaccine; pneumococcal vaccine; and internet usage. The survey was conducted in November 2017 and data analysis was performed in December 2017.

Research results
A total of 138 respondents aged 20 to 59 (median 25.6) years with a male to female ratio of 2.5 participated in the survey. Only 11.6% (16/138) participants reported receiving all three vaccines, 15.2% (21/138) did not receive any vaccine, 78.1% (105/138) received meningococcal, 68.1% (94/138) influenza and 13.8% (19/138) pneumococcal vaccine. Females were more likely to receive a vaccine than males (OR 3.6, 95%CI: 1.0-12.7, P < 0.05). Willingness to follow health authority’s recommendation was the main reason for receipt of vaccine (78.8%) while believing that they were up-to-date with vaccination (39.8%) was the prime reason for non-receipt.

Research conclusions
This survey shows that many HCWs at Hajj miss out the compulsory and highly recommended vaccines; lack of awareness is a key barrier and authority’s advice is an important motivator.

Research perspectives
Achieving satisfactory vaccination coverage among local HCWs at Hajj remains a challenge. Health education followed by stringent measures may be required to improve their vaccination rate. Evaluation of the role of workplace vaccination campaigns and the Basic Infection Control Skills License should be considered to better understand the uptake of vaccination among HCWs at Hajj.

ACKNOWLEDGEMENTS
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Sex and gender differences in travel-associated disease.


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SECTION C: CLINICAL TRIALS

Chapter 4: Impact of quadrivalent meningococcal ACWY vaccines on meningococcal carriage

Nasopharyngeal carriage is the primary source of transmission and colonisation of the human pharynx is essential for the meningococcus to survive since the human pharyngeal mucosa is its only reservoir [92]. In addition, pharyngeal colonisation is the inevitable first stage prior to the development of invasive disease.

The previous chapter demonstrated suboptimal vaccination coverage among both key domestic groups (pilgrims and health care workers). One possible way to compensate for this is to assess and, if possible, limit meningococcal carriage (i.e. induce sufficient herd immunity). The conjugate vaccines are believed to be capable of reducing carriage but no head to head trial has been conducted to compare this with polysaccharide vaccines. This chapter reports on the results of a randomised controlled trial aimed primarily to compare the effects of conjugate versus polysaccharide meningococcal quadrivalent ACWY vaccine on nasopharyngeal carriage among mostly domestic Hajj pilgrims, and secondarily to assess meningococcal carriage before and after Hajj.

What is the context?
- The conjugate vaccines are believed to be capable of reducing carriage but no head to head trial has been conducted to compare this with polysaccharide vaccines.

What is new?
- A randomised, controlled trial to compare MenACWY-C vaccine with MenACWY-PS vaccine among Hajj pilgrims to investigate whether the conjugate vaccine is more effective in reducing asymptomatic carriage of meningococci, and whether any effect may be long-standing.

What is the impact?
- The near-absence of detectable meningococcal carriage among Hajj pilgrims neither supports nor refutes the superiority of meningococcal conjugate ACWY vaccine over the polysaccharide vaccine against carriage.
- A further adequately powered assessment in other endemic settings is needed.
Impact of quadrivalent meningococcal ACWY vaccines on meningococcal carriage among Hajj pilgrims: A randomised trial

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Impact of quadrivalent meningococcal ACWY vaccines on meningococcal carriage among Hajj pilgrims: A randomised trial

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Abstract

**Background:** Intense congestion during the Hajj pilgrimage amplifies the risk of meningococcal carriage and disease, and there have been many meningococcal outbreaks reported amongst pilgrims. Thus, a strict vaccination policy is enforced by the host country and either polysaccharide or conjugate quadrivalent meningococcal vaccines are mandatory. However, unlike conjugate vaccines, the polysaccharide vaccine is not thought to reduce pharyngeal carriage of meningococci.

**Methods:** A single-blinded, randomised, controlled trial amongst pilgrims from Saudi Arabia and Australia during the Hajj seasons of 2016-2017 was conducted to compare MenACWY-Conjugate vaccine with MenACWY-Polysaccharide vaccine, to determine if the conjugate vaccine is more effective in reducing asymptomatic carriage of meningococci, and whether the effect may be long-standing. Oropharyngeal swabs were obtained pre-, immediately post-, and 6-11 months following completion of Hajj and tested for the presence of meningococci.

**Results:** 1146 participants aged 18–91 (mean 37.6) years were randomised to receive either the polysaccharide (n=561) or conjugate (n=561) vaccine, 60.8% were male, and 93.5% were from Saudi Arabia. Among oropharyngeal swabs obtained before Hajj, only two tested positive for *Neisseria meningitidis*. Similarly, meningococci were identified in only one sample at each of the post-Hajj and late follow-up visits. A *post hoc* analysis of the third swabs revealed that 22.4% of all participants (50/223) were positive for *Streptococcus pneumoniae* nucleic acid.

**Conclusion:** The low overall carriage rate of meningococci found among Hajj pilgrims in 2016 and 2017 demonstrates a successful vaccination policy, but neither supports nor
refutes the superiority of meningococcal conjugate ACWY vaccine over the polysaccharide vaccine against carriage.

**Key words:** Hajj, meningococcal carriage, meningococcal conjugate vaccine, meningococcal polysaccharide vaccine, pneumococcal carriage
INTRODUCTION

Intense congestion, including shared accommodation and compromised hygiene, during mass gatherings (MGs) such as the Hajj pilgrimage amplify the risk of meningococcal carriage and disease.\(^1\) Intercontinental spread of serogroup A meningococcal disease in 1987 and serogroup W disease in 2000 and 2001 affected thousands of Hajj pilgrims globally.\(^1\)\(^-\)\(^5\) Compulsory bivalent (serogroups A and C) vaccination appeared to control the disease during the 1990s. After fresh outbreaks of serogroup W disease were associated with the Hajj in 2000 and 2001, quadrivalent meningococcal serogroups A, C, W and Y (MenACYW) vaccination became mandatory for attending Hajj since 2002, and was associated with control of the outbreaks.\(^6\)\(^,\)\(^7\)

Reported rates of asymptomatic meningococcal carriage vary, and can be relatively high among Hajj pilgrims;\(^8\)\(^-\)\(^11\) ranging from 0% among Thai pilgrims in 2001 to 27% among Turkish pilgrims in 2010.\(^12\)\(^,\)\(^13\) In addition, about half of Singaporean Hajj pilgrims and their household contacts who were carriers of serogroup W meningococci immediately after Hajj remained carriers for about six months.\(^14\) Since 100% vaccine coverage or the use of appropriate vaccines\(^15\)\(^-\)\(^17\) cannot be guaranteed despite vigorous campaigns,\(^18\)\(^-\)\(^21\) a vaccine capable of eradicating carriage in order to prevent transmission of meningococci and occurrence of meningococcal disease in high risk settings such as Hajj is important. The plain polysaccharide vaccine is not expected to reduce pharyngeal carriage of meningococci;\(^22\) whereas conjugate vaccines have been shown to reduce long term meningococcal carriage\(^23\) and provide long-lasting immunity.\(^24\) The quadrivalent meningococcal conjugate vaccine has been shown to reduce carriage over 12 months in adults aged 18-24 years,\(^23\) and provides extended immunity in adolescents for at least five years.\(^25\) Among university students in the United Kingdom, three months post vaccination...
with MenACWY conjugate (MenACWY-C) vaccine there was significantly lower carriage of vaccine serogroups in the MenACWY-C group compared with controls (serogroup B [4CMenB] or Japanese Encephalitis vaccine recipients): 39% (95% confidence interval (CI) 17.3 - 55.0) carriage reduction for serogroup Y and 36.2% (95% CI 15.6 - 51.7) carriage reduction for serogroups C, W, and Y combined. Additionally, in an observational study involving Polish soldiers, meningococcal carriage was found to be significantly lower among soldiers vaccinated with a quadrivalent conjugate vaccine compared to those who were not vaccinated (1.2% [3/257] versus 9.6% [29/302], \( p < 0.01 \)). However, there are few studies that have directly compared the effect of conjugate vaccines to polysaccharide vaccines on pharyngeal carriage of meningococci, and there are no prior studies comparing meningococcal carriage rates among Hajj pilgrims following MenACWY-C and MenACWY polysaccharide (MenACWY-PS) vaccination.

The official recommendation from the Saudi Arabian Ministry of Health favours the use of conjugate vaccines when available, although either polysaccharide or conjugate vaccines are accepted. However, in resource-poor settings the polysaccharide vaccine is still widely used. Studies conducted in recent years show that only a minority (0.2%) of Hajj pilgrims receive MenACWY-C vaccine, although this proportion will likely change in the future as most resource-rich countries have now switched to greater use of conjugate vaccines.

A well-powered carriage study among Hajj pilgrims could inform renewed policy on meningococcal vaccination for Hajj pilgrims as well as for attendees of other large MGs. Therefore, we conducted a randomised, controlled trial to compare MenACWY-C vaccine with MenACWY-PS vaccine among pilgrims from Saudi Arabia and Australia during the 2016-2017 Hajj seasons, to investigate whether the conjugate vaccine is more effective than
the polysaccharide vaccine in reducing asymptomatic carriage of meningococci, and
whether any effect may be long-standing.

Materials and Methods

Study design and objectives

A multicentre, single-blinded, randomised controlled trial with two study arms was
conducted during two Hajj seasons: April 2016 to May 2017 in Australia spanning the 2016
Hajj season; and August 2017 to August 2018 in Saudi Arabia spanning the 2017 Hajj
season (Figure 1). The primary objectives were to compare the prevalence of serogroup-
specific meningococcal carriage among Hajj pilgrims receiving MenACWY-C vaccine to
that among those receiving MenACWY-PS vaccine within sixty days, and again at 6-11
months after Hajj completion.

Written informed consent was obtained from each participant. Ethics approval was
granted by the University of Sydney Human Research Ethics Committee (HREC),
Australia (Ref: 2015/693), the Sydney Children's Hospitals Network Human Research
Ethics Committee (Ref: HREC/16/SCHN/209), the Institutional Review Board of King
Abdullah Medical City, Saudi Arabia (Ref: 16-266) and the Directorate of Health Affairs,
Ministry of Health, Jeddah, Saudi Arabia (Ref: A00484). The trial was registered with the
Australian New Zealand Clinical Trials Registry: ACTRN12616001230448 (full protocol
available online).

Participants and randomisation

Adults aged 18 years or older who were planning to attend Hajj and able to provide
informed consent were recruited from Greater Sydney, New South Wales, Australia, and
from Jeddah and Makkah, Makkah province, Saudi Arabia. Supplementary text 1 provides a detailed description of the recruitment process. Exclusion criteria included any prior receipt of MenACWY-C vaccine, receipt of MenACWY-PS vaccine in the previous three years, any immunodeficiency condition or long-term receipt of immunosuppressant medication, or previous history of meningococcal disease. Individuals with a history of systemic antibiotic use were temporarily excluded until after a lapse of seven days from the last dose. Those who received antibiotics during or after Hajj were retained in the trial; however, a delayed swab (one week after completing antibiotics) was attempted when practical, otherwise they were excluded from the ‘per-protocol’ analysis.

A computer-based random assignment was used to allocate participants from Saudi Arabia into one of two study groups with a 1:1 ratio. Due to a temporary stock-out of one of the study vaccines, group allocation in Australia was based on timing of the first visit; those who attended April sessions were assigned to Group A, and those who attended during May to July were assigned to Group B. Group A received MenACWY-C. A tetanus toxoid (TT) conjugated vaccine (Nimenrix™, GlaxoSmithKline) was used in Australia and a CRM197–conjugated vaccine (Aramen™, Arabio) was used in Saudi Arabia. Group B received MenACWY-PS (Mencevax™ ACWY, GlaxoSmithKline). Participants and investigators were masked to group assignment until the conclusion of the study. Research assistants and nurses who prepared and administered the vaccines did not take part in any of the outcome assessments.

Sample collection, storing and transportation

Each participant provided three swab samples obtained from the posterior oropharyngeal wall (Figure 1). A baseline swab was collected from all participants prior to Hajj followed
by receipt of their allocated vaccine. A second swab was collected within sixty days after completion of Hajj, and a third swab was collected six to 11 months after completion of Hajj. In Australia, M40 TransystymTM (COPAN ITALIA S.P.A., Brescia Lombardy, Italy) swabs were used, and were immediately placed in transport medium, inoculated onto inhouse prepared Lysed Blood (LB) agar, and Vancomycin, Colistin, Nystatin and Trimethoprim (VCNT) agar plates within four hours of collection. Within eight hours of collection, the inoculated plates were delivered to the World Health Organisation Collaborating Centre and Neisseria Reference Laboratory, Randwick, New South Wales (NSW), Australia.

In Saudi Arabia, the pre- and post-Hajj samples were immediately placed in Stuart transport medium, delivered to Al Borg Medical Laboratory, Jeddah, Saudi Arabia within six hours of collection and directly inoculated onto modified Thayer-Martin (TM) medium.

The late follow up (third) swabs collected from participants in Saudi Arabia were placed in universal transport medium (UTM; Vircell Microbiologists, Granada, Spain) promptly and stored at -80°C until shipped frozen to the institute of Clinical Pathology & Medical Research (ICPMR), Westmead, NSW, Australia.

**Laboratory procedures**

In Australia, inoculated LB and VCNT plates were incubated at 37°C with ~5% CO₂ and 80-90% humidity for 18-24 hours. Presumptive identification of *N. meningitidis* was based on the use of matrix assisted laser desorption/ionisation - time of flight (MALDI-TOF) analysis for all Gram-negative diplococci, coco-bacilli or cocci isolated. Confirmation of *N. meningitidis* was based on latex particle agglutination assay by two commercial kits:
Pastorex™ (Bio-Rad Laboratories Inc., Marne-La-Coquette, France) for serogroups A, B or C and monoclonal antiserum (Remel, Lenexa, KS, USA) for identification of serogroups W or Y. Confirmatory genotyping and genogrouping was performed by polymerase chain reaction (PCR) at St. George Hospital, Kogarah, NSW, Australia. Other biochemical tests were performed using Minibact-N™ kit (SSI Diagnostica, Hillerød, Denmark) for confirmation of non-groupable N. meningitidis.

In Saudi Arabia, inoculated TM plates were incubated at 35-37°C with ~5% CO₂ and observed daily for up to 72 hours for the appearance of typical meningococcal colonies. A commercial identification system, VITEK™ 2 (bioMérieux, Inc. Marcy-l’Étoile, France), was used for presumptive identification of isolated organisms, and confirmed using a second commercial kit system API NH™ (bioMérieux, Inc. Marcy-l’Étoile, France).

Serogroups were determined using slide agglutination tests with anti-sera against serogroups A, C, Y and W performed on young subcultures.

In hope of better sensitivity to detect meningococcal carriage, nucleic acid (NA) testing was carried out on the third swabs obtained from participants in Saudi Arabia in place of standard culture. The MagNA Pure 96 DNA and Viral NA SV Kit on Roche™ MagNA Pure 96 System was used to extract the NA. N. meningitidis NA was detected by PCR using the cerebrospinal fluid (CSF) 16-WELL (REF. 27050) multiplex PCR assay (AusDiagnostics Pty Ltd, Mascot, New South Wales, Australia). Post hoc NA testing was also performed concurrently on these swabs to detect the presence of S. pneumoniae to exclude any role of poor sampling and processing in the absence of detectable meningococcal carriage. Any samples positive for S. pneumoniae were confirmed using an in-house S. pneumoniae PCR assay. These assays were chosen for their ability to sensitively detect small numbers of N. meningitidis and S. pneumoniae organisms in meningitis cases.
Statistical analyses

Conjugate MenC vaccines have been shown to reduce carriage of serogroup C meningococci by at least 75%.29 Thus, assuming 3% carriage (against any one serogroup) among Hajj pilgrims immunised with a polysaccharide vaccine, a sample size of 567 per arm would be needed to achieve 80% power with 95% CI (two-sided $\alpha = 0.05$) to show a 75% reduction in carriage in the conjugate vaccine arm compared to the polysaccharide vaccine arm. To account for 20% loss to follow-up, approximately 1420 pilgrims were planned to be recruited.

Data were initially entered into a web-based form hosted by Wufoo™ (SurveyMonkey Inc., San Mateo, CA, USA) and subsequently exported into a Microsoft Excel™ 2016 (Microsoft Corp., Redmond, WA, USA) spreadsheet. IBM Statistical Package for the Social Sciences (SPSS) for Windows, version 25 (IBM Corp., Armonk, NY, USA) was used to import and analyse the data.

RESULTS

Over two thousand individuals were approached, of whom 1146 agreed to participate in the study and were randomised to one of the two study arms. Group assignment of 24 participants was inadequately documented and these individuals were excluded from the comparative analyses but retained for the remaining analyses (Figure 1).

The participants were aged 18–91 (mean 37.6) years, 60.8% were male, and 93.5% were pilgrims from Saudi Arabia (domestic pilgrims). The mean age and prevalence of chronic illnesses were higher among Group B participants ($p<0.002$). There were no differences in other demographic and baseline characteristics between groups as shown in Table 1.
Among the oropharyngeal swabs obtained before Hajj, only two tested positive for *N. meningitidis* carriage. Similarly, meningococci were identified in only one sample at each post-Hajj and late follow up visits (Table 2). One participant from the Australian cohort was carrying serogroup B meningococci before Hajj, no meningococcal carriage was identified from his post-Hajj sample but a non-groupable strain was identified in the late follow-up visit. The other two culture-positive samples (non-groupable meningococci) were from two different participants from Saudi Arabian, one pre- and one post-Hajj. No meningococci were detected by PCR, among the 223 late follow up swabs collected from participants from Saudi Arabia.

In contrast, *post hoc* analysis of the third swabs revealed that 22.4% (50/223) of these late follow up samples were positive for *S. pneumoniae* by PCR (18.7% [20/107] of Group A and 26.4% [29/110] of Group B).

**DISCUSSION**

This appears to be the first study assessing the short-to-medium term meningococcal pharyngeal carriage following Hajj among principally domestic pilgrims. The key finding is that the prevalence of meningococcal carriage before, immediately after and six to 11 months after Hajj completion was almost zero. This finding, which is reassuring from a public health perspective, hindered the ability to answer the main study question of whether MenACWY-C vaccine is better than MenACWY-PS in reducing pharyngeal carriage of meningococci.

The reported prevalence of meningococcal carriage following Hajj varies between studies and zero or near-zero carriage rates have been reported previously.\(^9,12,30,31\) In 2001, Phrom-in reported no meningococcal carriage in a cross-sectional study among Thai
Similarly, a pilot study among Australian pilgrims conducted by our team found a very low carriage rate of 0.02% in 2012. Two other studies reported <1% carriage rate among mixed international pilgrims (0.15%), and among Makkah and Jeddah residents (0.8%) in 2001 just before the implementation of the quadrivalent vaccination policy. Additionally, two studies have reported the absence of meningococcal carriage from throat swabs obtained from Iranian and Kuwaiti pilgrims in 2003 and 2005 respectively, however, all of the Iranian and 83% of the Kuwaiti participants had a history of ciprofloxacin receipt. A recent study involving 229 Turkish pilgrims who received TT-conjugated MenACWY-C vaccine ahead of the 2018 Hajj found a carriage rate of 3.9% (9/229) before travel and a carriage rate of 0.4% (1/229) after travel but the effect could not be attributed to vaccination as all carriage isolates were meningococcal serogroup B. In contrast, a high carriage rate of 27% and 17% respectively was reported after Hajj in 2010 among returning Turkish pilgrims and in 2001 among pilgrims from Singapore. Other studies have reported rates ranging between 2.6% and 6.3%. Several theories could explain these different findings. Importantly, there is wide variability in the study designs, particularly the duration of time between the Hajj peaks (days nine and ten of the month of Dhul-Hijjah when all pilgrims gather in specific confined areas for several hours) and swab collection, as well as accounting for receipt of antibiotics or meningococcal vaccine as a confounder in some studies. Furthermore, the ‘seasonal dynamics’ of bacterial meningitis may play a role as Hajj is based on a lunar calendar meaning that there is a date shift every year and the Hajj period moving between the four annual seasons. Previous studies were also conducted among international pilgrims whose Hajj experience is different to that of domestic pilgrims in many respects that limits the exposure of
domestic pilgrims to the risk factors that Hajj may pose. Pilgrims from Makkah and Jeddah, who formed 93% of our sample, have specific characteristics in regard to their Hajj experience which is usually very short (up to five nights) and does not begin or end with long-distance travel, including flights and passing through crowded airport terminals. In addition, domestic pilgrims reside in designated areas at the peripheral zone of the Hajj site in Mina, which are less crowded, and many pilgrims from Makkah and Jeddah remain at home during most of the Hajj rites. They are also less likely to participate in crowded walking rites during the Hajj as they travel by trains, and even postpone some other key rituals at crowded sites until after completion by international pilgrims.

The possibility of poor swabbing technique, and limited sensitivity of culture to detect meningococcal carriage exist; however, the likelihood of this is reduced given the detection of a high prevalence of pneumococcal carriage from the third swabs from which no meningococci were detected. Since swabs were not tested for \textit{S. pneumoniae} before Hajj or immediately following Hajj (at the first two study visits) we cannot establish a relationship between Hajj and pneumococcal carriage. Furthermore, the prevalence of pathogenic serotypes could not be assessed in the current trial as no serotyping test was done for \textit{S. pneumoniae}.

The absence of detectable oropharyngeal carriage of meningococci in this study may be suggestive of a successful vaccination policy. It has been demonstrated that the mean annual incidence of IMD in Saudi Arabia decreased significantly between 1995-1999 and 2002-2011 from 0.20/100,000 (SD ±0.1) to 0.06/100,000 (SD ±0.06) which has been attributed to the effect of the mandatory ACWY vaccination for Hajj pilgrims and residents in Makkah and Madina.\textsuperscript{6} Additionally, the introduction of the MenACWY-C vaccine into the Saudi National Immunisation Program in 2013 may also have contributed
to halting the transmission of meningococci in the community. Further, by examining data from the Singapore Ministry of Health, Wilder-Smith and colleagues demonstrated that no more Hajj-associated meningococcal W cases occurred in Singapore from 2002 to 2008\textsuperscript{43}. Resource constraints, including the inability to secure vaccines for the study, were a major limitation of the study that resulted in an ‘on the spot recruitment’ strategy in Saudi Arabia, inviting and recruiting pilgrims when they arrived at primary health care centres to receive their Hajj vaccines. This resulted in both a failure to achieve the proposed sample size and significant loss to follow up of participants.

Obtaining oropharyngeal rather than nasopharyngeal swabs, for the purposes of technical ease for research staff, is another limitation. However, the high rate of positivity for \textit{S. pneumoniae}, which like \textit{N. meningitidis} also primarily colonises the nasopharynx, from the oropharyngeal swabs is reassuring and suggests that sampling the nasopharynx may not have made a significant difference to the overall findings of the study. The use of different microbiological techniques at different time-points is also a potential confounder with PCR testing of the third swabs added \textit{post hoc} during the trial. Future research should incorporate both conventional and molecular microbiological detection methods at all time-points to ensure valid comparisons can be made longitudinally. Other limitations, such as difficulties with the randomisation process were unlikely to have any significant impact on the study findings given that meningococcal yield was near zero in all participants.

In conclusion, the near-absence of detectable meningococcal carriage among all participants in this trial could be suggestive of a successful vaccination policy or may due to seasonal/temporal variability. This limited our ability to draw any conclusions on the
efficacy of either the MenACWY-PS or the MenACWY-C vaccines in reducing pharyngeal carriage.

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Prof R.B. has received funding from Baxter, CSL, GSK, Merck, Novartis, Pfizer, Roche, and Sanofi Pasteur for the conduct of sponsored research, travel to present at conferences or consultancy work; all funding received is directed to research accounts at the Children’s Hospital at Westmead. Dr H.R. has received fees from Pfizer, Sanofi and Novartis for consulting or serving on an advisory board. The other authors have declared no conflict of interest in relation to this work.
AUTHOR CONTRIBUTIONS

H.R., A.K., M.M.L., A-M.B., O.B. and R.B. conceived the study and designed the study protocol; A-M.B., O.B., M.T., M.A., M.I.A., H.B. and Hajj research team members carried out recruitment, vaccination, swab sampling and data collection under the supervision of H.R. and M.A.B.; O.S., N.J., J.K., M.M.L. and D.E.D. carried out the laboratory work, A-M.B. and M.A. carried out analysis and interpretation of the data; A-M.B., H.R., and A.K. prepared the first draft of the manuscript; all authors critically revised the manuscript for intellectual content, read and approved the final version. H.R. is the guarantor of the manuscript.

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acwy glycoconjugate or a serogroup b meningococcal vaccine on meningococcal carriage:


Figure 1. Project timeline
### Table 1. Baseline demographic characteristic of participants

<table>
<thead>
<tr>
<th></th>
<th>All (n=1146)*</th>
<th>Group A (n=561)</th>
<th>Group B (n=561)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>Mean ± S.D. (range)</td>
<td>37.6 ± 12.1 (18-91)</td>
<td>36.5 ± 11.5 (18-81)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>697 (60.8%)</td>
<td>345 (61.5%)</td>
<td>344 (61.3%)</td>
</tr>
<tr>
<td>Female</td>
<td>449 (39.2%)</td>
<td>216 (38.5%)</td>
<td>217 (38.7%)</td>
</tr>
<tr>
<td><strong>Site of recruitment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>1071 (93.5%)</td>
<td>531 (94.7%)</td>
<td>516 (92.0%)</td>
</tr>
<tr>
<td>Australia</td>
<td>75 (6.5%)</td>
<td>30 (5.3%)</td>
<td>45 (8.0%)</td>
</tr>
<tr>
<td><strong>City of residence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jeddah</td>
<td>884 (76.9%)</td>
<td>436 (77.7%)</td>
<td>430 (76.6%)</td>
</tr>
<tr>
<td>Makkah</td>
<td>187 (16.6%)</td>
<td>95 (16.9%)</td>
<td>86 (15.3%)</td>
</tr>
<tr>
<td>Sydney</td>
<td>75 (6.5%)</td>
<td>30 (5.3%)</td>
<td>45 (8.0%)</td>
</tr>
<tr>
<td><strong>Country of origin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>551 (49.6%)</td>
<td>273 (50.0%)</td>
<td>265 (49%)</td>
</tr>
<tr>
<td>Egypt</td>
<td>216 (19.4%)</td>
<td>104 (19.0%)</td>
<td>109 (20.1%)</td>
</tr>
<tr>
<td>Pakistan</td>
<td>83 (7.5%)</td>
<td>36 (6.6%)</td>
<td>44 (8.1%)</td>
</tr>
<tr>
<td>Yemen</td>
<td>54 (4.9%)</td>
<td>31 (5.7%)</td>
<td>23 (4.3%)</td>
</tr>
<tr>
<td>India</td>
<td>49 (4.4%)</td>
<td>24 (4.4%)</td>
<td>24 (4.4%)</td>
</tr>
<tr>
<td>Jordan</td>
<td>41 (3.7%)</td>
<td>26 (4.8%)</td>
<td>13 (2.4%)</td>
</tr>
<tr>
<td>Syria</td>
<td>21 (1.9%)</td>
<td>5 (0.9%)</td>
<td>15 (2.8%)</td>
</tr>
<tr>
<td>Palestine</td>
<td>18 (1.6%)</td>
<td>6 (1.1%)</td>
<td>12 (2.2%)</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>13 (1.2%)</td>
<td>13 (2.4%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Sudan</td>
<td>12 (1.1%)</td>
<td>6 (1.1%)</td>
<td>6 (1.1%)</td>
</tr>
<tr>
<td>Lebanon</td>
<td>9 (0.8%)</td>
<td>2 (0.4%)</td>
<td>6 (1.1%)</td>
</tr>
<tr>
<td>Australia</td>
<td>7 (0.6%)</td>
<td>0 (0.0%)</td>
<td>7 (1.3%)</td>
</tr>
<tr>
<td>Indonesia</td>
<td>7 (0.6%)</td>
<td>4 (0.7%)</td>
<td>3 (0.6%)</td>
</tr>
<tr>
<td>Philippines</td>
<td>7 (0.6%)</td>
<td>3 (0.5%)</td>
<td>4 (0.7%)</td>
</tr>
<tr>
<td>Other</td>
<td>23 (2.3%)</td>
<td>13 (2.4%)</td>
<td>10 (2.0%)</td>
</tr>
<tr>
<td><strong>Chronic illnesses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>80 (7.0%)</td>
<td>25 (4.5%)</td>
<td>54 (9.6%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>71 (6.2%)</td>
<td>21 (3.7%)</td>
<td>49 (8.7%)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>14 (1.2%)</td>
<td>4 (0.7%)</td>
<td>10 (1.8%)</td>
</tr>
<tr>
<td>Asthma</td>
<td>11 (1.0%)</td>
<td>6 (1.1%)</td>
<td>5 (0.9%)</td>
</tr>
<tr>
<td>Other</td>
<td>26 (2.5%)</td>
<td>11 (2.1%)</td>
<td>15 (2.9%)</td>
</tr>
<tr>
<td>No chronic illness</td>
<td>984 (85.9%)</td>
<td>502 (89.5%)</td>
<td>459 (81.8%)</td>
</tr>
</tbody>
</table>

*The assigned group could not be determined for 24 participants.

**The country of origin of 35 participants is unknown.
Table 2. Prevalence of *N. meningitidis* carriage overall and by study groups among participants from Saudi Arabia and Australia

<table>
<thead>
<tr>
<th>Visit</th>
<th>Overall</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All subjects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Hajj*</td>
<td>2/1133 (0.2)</td>
<td>0/554 (0)</td>
<td>2/557 (0.4)</td>
</tr>
<tr>
<td>Post-Hajj^</td>
<td>1/745 (0.1)</td>
<td>1/358 (0.3)</td>
<td>0/375 (0)</td>
</tr>
<tr>
<td>Late follow-up~</td>
<td>1/255 (0.4)</td>
<td>0/116 (0)</td>
<td>1/138 (0.7)</td>
</tr>
<tr>
<td><strong>Saudi Arabia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Hajj*</td>
<td>1/1059 (0.1)</td>
<td>0/525 (0)</td>
<td>1/512 (0.2)</td>
</tr>
<tr>
<td>Post-Hajj^</td>
<td>1/683 (0.1)</td>
<td>1/332 (0.3)</td>
<td>0/338 (0)</td>
</tr>
<tr>
<td>Late follow-up~</td>
<td>0/220 (0.0)</td>
<td>0/104 (0)</td>
<td>0/115 (0)</td>
</tr>
<tr>
<td><strong>Australia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Hajj*</td>
<td>1/74 (1.4)</td>
<td>0/29 (0)</td>
<td>1/45 (2.2)</td>
</tr>
<tr>
<td>Post-Hajj^</td>
<td>0/62 (0)</td>
<td>0/25 (0)</td>
<td>0/37 (0)</td>
</tr>
<tr>
<td>Late follow-up~</td>
<td>1/36 (2.8)</td>
<td>0/13 (0)</td>
<td>1/23 (4.3)</td>
</tr>
</tbody>
</table>

Group A: received MenACWY conjugate vaccine, Group B received MenACWY polysaccharide vaccine. * 7-90 days before Hajj, ^1-60 days after Hajj, ~6-11 months after completion of Hajj.
Figure 1. Project timeline

First Visit
(7-90 days before Hajj)

- Screened
  \( n \approx 2000+ \)

- Enrolled and randomised
  (\( n=1146 \))

  Group A
  (conjugate)
  Completed visit and vaccinated (\( n=561 \))
  Valid swabs (\( n=554 \))

  Group B
  (Polysaccharide)
  Completed visit and vaccinated (\( n=561 \))
  Valid swabs (\( n=557 \))

- Uncertain randomisation
  (\( n=24 \))

- On antibiotics (\( n=1 \))
- Fear of swab (\( n=1 \))
- Not eligible (\( n=1 \))
- Out of stock (\( n=1 \))
- Missing samples (\( n=3 \))

Hajj Pilgrimage
(12-17 September 2016 and 1-6 September 2017)

- Six months later

Second Visit
(1-60 days after Hajj)

- Completed visit (\( n=362 \))
- Valid swabs (\( n=358 \))

- Completed visit (\( n=378 \))
- Valid swabs (\( n=375 \))

- On antibiotics (\( n=1 \))
- Missing samples (\( n=3 \))

Third Visit
(6-11 Months)

- Completed visit (\( n=130 \))
- Valid swabs (\( n=116 \))

- Completed visit (\( n=148 \))
- Valid swabs (\( n=138 \))

- Missing samples (\( n=10 \))

- On antibiotics (\( n=2 \))
- Missing samples (\( n=2 \))
Chapter 5: Meningococcal Conjugate Vaccines and Immune Interference

Immune interference between conjugate vaccines themselves or between their protein components and other vaccines containing the same proteins as antigen is a current issue [62]; especially so with the growing number of conjugate vaccines available and countries that have replaced plain polysaccharide vaccines with their conjugate counterpart in recent years [93, 94]. This is of particular interest when multiple vaccines are to be administered in a short period of time such as the case with travellers, including Hajj pilgrims. This section addresses this issue and compares the immune response to MenACWY conjugate vaccine when administered prior to, concurrent with or subsequent to a diphtheria-tetanus containing vaccine, namely Tdap.
5.1 Interaction of meningococcal conjugate vaccines with other vaccines


What is the context?
- Travellers and Hajj pilgrims are often required to receive multiple vaccinations within a short time period.
- These vaccines include conjugate vaccines which may interfere with diphtheria-tetanus containing vaccines.

What is new?
- A Letter-to-editor to highlight the issue among travellers focussing on meningococcal conjugate vaccines.

What is the impact?
- Concurrent administration is recommended.
- If separate administration of vaccines is required or requested, it is better to give meningococcal conjugate vaccines first.
Letter to the Editor

Interaction of meningococcal conjugate vaccines with other conjugate or diphtheria–tetanus containing vaccines

Al-Mamoon Badahdah\textsuperscript{1,2,3}, Mohamad Tashani\textsuperscript{2,4}, Ameneh Khatami\textsuperscript{2}, Robert Booy\textsuperscript{1,2,5}, and Harunor Rashid\textsuperscript{1,2,5}*

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Submitted 14 October 2018; Revised 19 October 2018; Editorial decision 21 October 2018; Accepted 23 October 2018

Key words: Carrier protein, diphtheria, meningococcal conjugate vaccine, tetanus, vaccine interaction

Certain travellers are required to receive meningococcal vaccines, e.g. Hajj pilgrims and those visiting the African meningitis belt during an epidemic. The use of meningococcal conjugate vaccines is growing, and globally replacing plain polysaccharide vaccines as they offer the advantage of better/longer-lasting immunity by converting the T-cell independent immune response to a T-cell dependent one. Polysaccharide–protein conjugate vaccines have the ability to induce both B- and T-cell responses and elicit more robust immunity and immunologic memory. The currently used meningococcal conjugate vaccines contain either tetanus toxoid (TT), a non-toxic cross-reactive material from diphtheria toxin (CRM\textsubscript{197}) or diphtheria toxoid (DT) as carrier proteins. These carrier proteins may interfere with diphtheria, tetanus and pertussis (DTP) containing vaccines that are routine in childhood. In addition, a booster dose of DTP containing vaccines is often used for adult travellers who were vaccinated more than 10 years previously.

The data on commercially available monovalent meningococcal serogroup C conjugate vaccines (MCC), demonstrate that the immunologic profile of the TT-conjugated MCC is superior to other vaccines that use CRM\textsubscript{197} as a carrier protein in terms of initial response, persistence of bactericidal antibody and priming for immune memory.\textsuperscript{1}

Currently, three quadrivalent meningococcal conjugate vaccines (containing serogroups A, C, W and Y; MenACWY), using DT (MenACWY-DT; Menevo\textsuperscript{\textregistered}, GlaxoSmithKline) or TT (MenACWY-TT; Nimenrix\textsuperscript{\textregistered}, Pfizer) as carrier proteins, are approved for use in different age groups. Although all three licensed MenACWY conjugate vaccines are available in Australia, the federal government chose to fund only the TT-conjugated MenACWY vaccine (over MenACWY-CRM\textsubscript{197} and MenACWY-DT) during the recent replacement of the combination Haemophilus influenzae type b (Hib)-MenC-TT vaccine administered at 12 months of age by MenACWY conjugate vaccine in the Australian national immunization program.

Conjugate MenACWY vaccines can be given concomitantly with most routine childhood and adolescent vaccines. However, our studies involving Australian Hajj pilgrims revealed a potential interaction that may occur between the carrier proteins and antigens or carrier proteins in other conjugate or combination vaccines containing tetanus or diphtheria upon concurrent or close administration (Table 1).\textsuperscript{2-4} Other studies have demonstrated various similar interactions between conjugate vaccines and other co-administered or closely administered vaccines\textsuperscript{1}; and the US Advisory Committee on Immunization Practices (ACIP) has recommended separate administration of MenACWY-DT and pneumococcal conjugate vaccines (PCV) due to possible interference in immune responses.

Unfortunately, the magnitude and the direction of these interactions are not always easy to predict, and many factors may be
involved (specific carrier proteins and type of polysaccharide used, other antigens involved, number of doses administered and timing).

Since travellers and pilgrims often have to receive more than one vaccine in a short period of time, it is important to consider potential interactions between vaccine components. For instance, if both conjugate MenACYW and PCV are required, when available, MenACWY-TT or MenACWY-CRM197 is preferred to MenACWY-DT. If MenACWY-TT or MenACWY-CRM197 are not available, ideally MenACWY-DT should be given at least 1 month after PCV. Generally, if multiple vaccinations with conjugate vaccines are required before travel, administering vaccines containing diphtheria or tetanus antigens concurrently produces adequate immune responses. However, if separating the vaccines was necessary, deferring the tetanus/diphtheria vaccine for several weeks after administering the conjugate vaccine is recommended as it avoids immune interference and offers the potential added advantage of an enhanced TT response.

Table 1. Summary of previous studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Vaccines used</th>
<th>Study group</th>
<th>Visit 1</th>
<th>Visit 2 (4 weeks after visit 1)</th>
<th>Change in MenACWY*</th>
<th>pneumococcal or DTaP antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tashani et al.1</td>
<td>- DTaP</td>
<td>A</td>
<td>DTaP</td>
<td>MenACWY-CRM197 + PCV13-CRM197</td>
<td>↓ GMTs to six serotypes of PCV13-CRM197b</td>
<td></td>
</tr>
<tr>
<td>- MenACWY-CRM197</td>
<td></td>
<td>B</td>
<td>DTaP + MenACWY-CRM197 + PCV13-CRM197</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- PCV13-CRM197</td>
<td></td>
<td>C</td>
<td>MenACWY-CRM197 + PCV13-CRM197</td>
<td>DTaP</td>
<td>↑ GMC of IgG against diphtheria pre-DTaPb</td>
<td></td>
</tr>
<tr>
<td>Tashani et al.3,4</td>
<td>- DTaP</td>
<td>A</td>
<td>DTaP</td>
<td>MenACWY-TT + PCV13-CRM197</td>
<td>↓ Proportion of subjects achieving a 4-fold rise in rSBA for serogroup W135</td>
<td></td>
</tr>
<tr>
<td>- MenACWY-TT</td>
<td></td>
<td>B</td>
<td>DTaP</td>
<td>MenACWY-TT + PCV13-CRM197</td>
<td>↑ GMCs of IgG to tetanus and diphtheria pre-DTaPb</td>
<td></td>
</tr>
<tr>
<td>- PCV13-CRM197</td>
<td></td>
<td>C</td>
<td>MenACWY-TT + PCV13-CRM197</td>
<td>DTaP</td>
<td>↑ IgG to tetanus post DTaPb</td>
<td></td>
</tr>
</tbody>
</table>

CRM197, non-toxic cross-reactive material of diphtheria toxin; DTaP, combination diphtheria, tetanus and acellular pertussis vaccine; GMC, geometric mean concentration; GMT, geometric mean titre; MenACWY, meningococcal serogroups A, C, W, Y; PCV13, 13-valent pneumococcal conjugate vaccine; rSBA, serum bactericidal assay using rabbit complement; TT, tetanus toxoid.

aChange in MenACWY antibody when using MenACWY-CRM197 and PCV13-CRM197 vaccine has not been reported.

bStatistically significant difference.

Conflict of interest: Professor Robert Booy has received funding from Baxter, CSL, GSK, Merck, Novartis, Pfizer, Roche, Romark and Sanofi Pasteur for the conduct of sponsored research, travel to present at conferences or consultancy work; all funding received is directed to research accounts at the Children’s Hospital at Westmead. Dr Harunor Rashid received fees from Sanofi, Pfizer and Novartis for consulting or serving on an advisory board. The other authors have no competing interests to declare.

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5.2 Interaction of quadrivalent meningococcal CRM$_{197}$-conjugate vaccine with diphtheria-tetanus containing vaccines

Publication #7: Mohamed Tashani, Al-Mamoon Badahdah, Mohammad Alfelali, Osamah Barasheed, Amani S. Alqahtani, Leon Heron, Melanie Wong, Jennifer Louth, Harunor Rashid, Ray Borrow, Robert Booy, Effect on meningococcal serogroup W immunogenicity when Tdap was administered prior, concurrent or subsequent to the quadrivalent (ACWY) meningococcal CRM$_{197}$-conjugate vaccine in adult Hajj pilgrims: A randomised controlled trial, Vaccine, 2019.

What is the context?

- Previous exposure to the protein component of a conjugate vaccine may enhance or suppress the immune response to the conjugate vaccine.

- A growing number of protein conjugated vaccines in routine vaccination schedules raises concerns for interaction.

- The case also applies to travellers and Hajj pilgrims who are often required to receive multiple vaccinations within a short time period.

What is new?

- An RCT to evaluate the immune response to meningococcal CRM$_{197}$-conjugate vaccine one month after being administered concurrently with Tdap, or 3-4 weeks prior to, or following Tdap.

What is the impact?

- Concurrent administration is both immunogenic and practical.

- Further evaluation of the effect of prior exposure to the carrier protein is suggested.
Effect on meningococcal serogroup W immunogenicity when Tdap was administered prior, concurrent or subsequent to the quadrivalent (ACWY) meningococcal CRM197-conjugate vaccine in adult Hajj pilgrims: A randomised controlled trial

Mohamed Tashani a,b,1, Al-Mamoon Badahdah a,c,d,*1, Mohammad Alfelali a,c,d, Osamah Barasheed e, Amani S. Alqahtani f, Leon Heron e, Melanie Wong g, Jennifer Louth h, Harunor Rashid a,c,h, Ray Borrow i, Robert Booy a,c,h,j

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Diphtheria, tetanus, acellular pertussis vaccine
Serum bactericidal antibody

A B S T R A C T

Immune responses to the capsular polysaccharide administered in the polysaccharide-protein conjugate vaccines can be either improved or suppressed by the pre-existence of immunity to the carrier protein. Receiving multiple vaccinations is essential for travellers such as Hajj pilgrims, and the use of conjugated vaccines is recommended.

We studied the immune response to meningococcal serogroup W upon prior, concurrent and sequential administration of a quadrivalent meningococcal conjugate vaccine (MCV4) conjugated to CRM197 (coadministered with 13 valent pneumococcal vaccine conjugate CRM197 [PCV13]), and tetanus-diphtheria-acellular pertussis (Tdap) vaccine in Australian adults before attending the Hajj pilgrimage in 2014.

Participants were randomly assigned, by computer-generated numbers, to three study arms by 1:1:1 ratio. Group A received Tdap followed by MCV4-CRM197 (+PCV13) 3–4 weeks later. Group B received all three vaccines in a single visit. Group C received MCV4-CRM197 (+PCV13) followed by Tdap 3–4 weeks later. Blood samples obtained prior to and 3–4 weeks after immunisation with MCV4-CRM197 were tested for meningococcal serogroup W-specific serum bactericidal antibody responses using baby rabbit complement (rSBA).

One hundred and seven participants aged between 18 and 64 (median 40) years completed the study. No significant difference in meningococcal serogroup W rSBA geometric mean titre (GMT) was observed between the study arms post vaccination with MCV-CRM197 but Group A tended to have a slightly lower GMT (A = 404, B = 984 and C = 1235, p = 0.15). No statistical difference was noticed between the groups in proportions of subjects achieving a ≥4-fold rise in rSBA titres or achieving rSBA titre ≥8 post vaccination.

In conclusion, receipt of MCV4-CRM197 vaccine prior, concurrent or subsequent to Tdap has similar immunologic response, and hence concurrent administration is both immunogenic and practical. However, further investigation into whether carrier induced suppression is a public health issue is suggested.

Clinical trial registration: ANZCTR no. ACTRN12613000536763.

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0264-410X/ © 2019 Elsevier Ltd. All rights reserved.
1. Introduction

Meningococcal disease and pneumococcal pneumonia are serious infections that affect the older population. Widespread childhood immunisation with conjugate vaccines in many developed countries has played a considerable role in terms of controlling disease and reducing mortality through direct and herd protection [1–4]. Conjugate vaccines surpass their polysaccharide counterparts as they are conjugated to carrier proteins responsible for converting the T-cell independent immunological response to T-cell dependent, thus provoking both B-cell and T-cell responses as well as establishing immunologic memory in all age groups [5]. The commonly used carrier proteins in licensed meningococcal polysaccharide-conjugate vaccines are: Diphtheria toxoid (DT), tetanus toxoid (TT) and non-toxic diphtheria toxin mutant protein (CRM197) [6].

The growing number of conjugate and multivalent vaccines has led to increasingly complex immunisation schedules. Experts recommend concomitant administration of several vaccines for higher compliance [7,8] as earlier evidence reported that separate injection of several vaccines significantly contributed to missed immunisation opportunities [9]. This raises concerns about compromising effectiveness due to unpredictable immunologic interference between components of routine vaccines and carrier proteins [10–12]. Concurrent or sequential immunisation with conjugate vaccines and their carrier protein (contained in diphtheria-tetanus-pertussis vaccines [DTP]) may either supress [13–15] or enhance [16–19] immune responses. A review of available evidence suggests that neither the carrier protein used nor its dose were able to explain or predict the observed interaction [12]. Thus, concurrent (or sequential administration) of conjugate vaccines may have positive as well as negative effects on their immunogenicity, and explanations of vaccine interactions are still lacking [12].

One occasion that may raise the concern of vaccine interference is the Hajj. The Hajj is a large annual mass gathering. Approximately 2.5 million Muslims from over 180 countries gather annually for a minimum 5-day period [20]. Intense congestion, shared accommodation and compromised hygiene amplify the risk of invasive meningococcal disease (IMD). Intercontinental Hajj related outbreaks of meningococcal serogroup A (MenA) occurred in 1987 [21], and of MenW in 2000–2001 [22]. Secondary cases of IMD have been reported in close contacts of returning pilgrims who may asymptptomatically carry meningococci [23–25]. Therefore, the Kingdom of Saudi Arabia Ministry of Health applied certain measures to secure the health of pilgrims at the Hajj [26,27], notably the declaration in 2001 that quadrivalent meningococcal vaccine against serogroups A, C, W, and Y is mandatory for all Hajj participants, with and after MCV4-TT injection (when Tdap was given first), we conducted this analysis to examine and compare the effect of sequential and concurrent administration of Tdap and MCV4-CRM197 on antibody against the MenW antigen among participants in the 2014 trial.

2. Material and methods

2.1. Study design

Open label randomised controlled trial conducted from the 1st February to 28th of June 2014 at The Children's Hospital at Westmead (CHW), Sydney, Australia.

2.2. Objectives

The primary objective was to establish whether prior, concurrent or subsequent use of Tdap, influences antibody responses to MCV4 and PCV13-CRM197. In this analysis, only the response to MenW antigen (contained in MCV4-CRM197) was examined as it was the only serogroup to demonstrate statistically significant difference in the previous study (using MCV4-TT) [35]. Diphtheria, tetanus and pneumococcal, antibody results as well as assessment of safety and reactogenicity have been reported previously [32].

2.3. Participants

Residents of Greater Sydney, New South Wales, Australia aged 18 years and older who were planning to travel to the Hajj and had the ability to provide written informed consent were invited, through Hajj tour groups, to participate in this study. Hajj travel agents sent their clients to CHW to enroll and receive the vaccine. Exclusion criteria were receipt of any vaccine containing meningococcal, pneumococcal, pertussis, diphtheria or tetanus antigens in the past three years, and known contraindications to any of the vaccines used in the trial as listed in the 10th edition of the Australian Immunisation Handbook [36].

2.4. Random assignment

By using computer-generated random serials, eligible participants were randomly assigned, by 1:1:1 ratio, to one of the three study arms according to the following (Fig. 1):

Group A: Vaccinated with Tdap (Boostrix®, GlaxoSmithKline) at first visit (left deltoid) then, 3–4 weeks later, followed by coadministration of MCV4-CRM197 (Menveo®, GlaxoSmithKline) and PCV13-CRM197 (Pneumа®, Pfizer) in the left deltoid and right deltoid muscles, respectively.

Group B: Concurrently vaccinated with Tdap in the left deltoid muscle and MCV4-CRM197 (lower right deltoid muscle) plus PCV13-CRM197 (upper right deltoid muscle).
Group C: Initially coadministered PCV13-CRM \(_{197}\) (in the right deltoid muscle) and MCV4-CRM \(_{197}\) (in the left deltoid muscle) followed by Tdap injection (in the left deltoid muscle) 3–4 weeks later.

2.5. Blood sample collection

A blood sample of 3 to 5 mL was collected at each study visit and also 3 to 4 weeks after receiving the last vaccine (Fig. 1). Samples were kept at +2 \(^\circ\)C to +8 \(^\circ\)C then, within 24 h, undergone centrifugation and serum was separated and was split into aliquots then stored in \(–80 \, ^{\circ}\)C freezer. Finally, samples obtained prior to and 3–4 weeks after immunisation with MCV4-CRM\(_{197}\) were delivered frozen to the Public Health England Vaccine Evaluation Unit, Manchester Royal Infirmary, Manchester, UK, for rSBA for serogroup W only as our previously published data have shown non-significant changes in meningococcal serogroup C and Y antibodies [35].

Subjects were considered as seropositive when having post vaccination rSBA titres \(\geq 8\) which correlates with protection against IMD [37]. Subjects were considered having achieved a seroresponse if their rSBA titre showed \(\geq 4\)-fold rise from pre-immunisation with MCV4-CRM\(_{197}\) to 3–4 weeks post-immunisation.

2.6. Statistical analysis

Data were assembled into a Microsoft Excel\textsuperscript{TM} 2016 spread sheet and imported to IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA) for analysis.

The principal outcome of interest was to compare the immunological responses to MenW component of the MCV4-CRM\(_{197}\) either administered concurrently or sequentially with Tdap. We have used a generalised linear model to calculate the geometric mean titres (GMTs) of rSBA titres and 95\% confidence intervals in order to analyse the difference in principal outcome among the study groups at time point of interest i.e. 3–4 weeks after immunisation with MCV4-CRM\(_{197}\). We have used the analysis of variance (ANOVA) to assay the log transformed rSBA titres. Chi square test was used to assess secondary endpoints across the study groups. This involved comparing proportions of subjects with rSBA titre \(\geq 8\) post vaccination (seropositive) and subjects achieving rSBA titers rise of \(\geq 4\)-fold from baseline to post immunisation (seroresponders).

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**Fig. 1. Subject disposition flowchart.** Group A: initially Tdap then MCV4 plus PCV13; Group B: administered all vaccines concurrently; Group C: MCV4 plus PCV13 then Tdap. MCV4: quadrivalent meningococcal CRM\(_{197}\) conjugate vaccine; PCV13: 13 valent pneumococcal CRM\(_{197}\)-conjugate vaccine; Tdap: combined tetanus, reduced diphtheria and acellular pertussis vaccine.
2.7. Ethics approval and trial registration

The Hunter New England Human Research Ethics Committee has assessed and approved this trial [Ref: 13/05/3.05]. The study conduction followed the Good Clinical Practice (GCP) guideline and International Conference on Harmonisation (ICH). The trial was registered on the Australian New Zealand Clinical Trials Registry (ANZCTR): ACTRN12613000536763.

3. Results

Of the 121 individuals assessed for eligibility, 107 complied with the protocol and completed the study (ten were not eligible, three withdrew as they could not follow the vaccination schedule and one participant belonging to Group B preferred not to continue because she developed fever and became mildly unwell) (Fig. 1). The detailed demographic characteristics and chronic conditions of the sample have been described previously [32]. Briefly, participants of the study were aged 18 to 64 years (median 40); 47 (44.8%) were males. Majority of them were born in Indonesia (n = 28), Pakistan (24), Australia (17), Lebanon (15) or Bangladesh (10).

rSBA titre results for *N. meningitidis* serogroup W are summarised in Table 1. There was no significant difference in MenW rSBA GMTs between the three study arms 3–4 weeks following the receipt of MCV4-CRM197 dose but giving Tdap after MCV4-CRM197 was suggestive of a slightly better response (A = 404, B = 984 and C = 1235, p = 0.15). Comparing the proportions of participants who achieved at least 4-fold increases in rSBA titre post-vaccination compared to prevaccination titre between the groups suggests no interference with MenW antibody response (p = 0.67) when Tdap was given 3–4 weeks before, after, or with MCV4-CRM197 + PCV13-CRM197: 82.9% of Group A subjects who received Tdap 3–4 weeks prior to MCV4-CRM197 + PCV13-CRM197; achieved rSBA titre rise of ≥4-fold in response to MenW compared to 88.6% of Group B (coadministered all vaccines at the same time) and 81.1% of Group C subjects (initially received MCV CRM197/PCV13-CRM197 followed by Tdap 3–4 weeks later).

The proportion of subjects with rSBA titre ≥8 (seropositive) for MenW after receiving MCV4-CRM197 + PCV13-CRM197 was also similar (p = 0.33) across the groups: Group A (82.9%), Group B (94.3%) and Group C (86.5%).

The assessment of tolerability of the vaccine had been previously published [32]. No serious adverse events were reported throughout the course of the trial.

4. Discussion

The study aimed to evaluate the immunogenicity of the MenW polysaccharide component of MCV4 conjugated to CRM197 (coadministered with PCV-CRM197), when administered before, with and after Tdap among adults. All three study arms had a similar immunological response in term of GMTs, seroresponse and seroprotection, with no statistical evidence of interference with or enhancement of the immunogenicity of the MenW polysaccharide but numbers were quite small. On the other hand, achievement of ≥4-fold rise in rSBA titres (seroresponse) to MenW was significantly lower, in the group exposed to prior Tdap 3–4 weeks, when a TT-conjugated MCV4 was used during the 2015 trial [35].

Results from other studies suggested that prior or concurrent exposure to diphtheria-tetanus containing vaccines does not affect the immune response to MCV4, which is consistent with our finding [14,38–40]. For instance, one trial showed that administration of MCV4-CRM197 prior to or simultaneously with Tdap did not alter its immunogenicity [38]. Another trial, in a study involving preschool and school age children, showed no effect on the immunogenicity of MCV4-CRM197 neither upon prior nor concurrent receiving of diphtheria-tetanus booster [14]. This non-inferiority was also observed when concurrent versus consecutive administration of MCV4-DT with Tdap was investigated in adolescents [39]. Additionally, a review of MCV4-TT showed also an intact immunogenicity upon concurrent administration in infants and toddlers with other vaccines including Tdap or 10-valent pneumococcal *Haemophilus influenzae* protein D conjugate vaccine (PCV10) [40].

On the other hand, a study involving adolescents observed a significantly lower proportion of seroresponders to MenW when Tdap was administered sometime before MCV4-CRM197 [38], which was consistent with our finding in the 2015 trial using MCV4-TT [35]. Furthermore studies revealed a suppression outcome in the Burrage trial where previous receipt of a tetanus containing vaccine reduced the immune response to meningococcal C vaccine conjugated to TT (MenC-TT) polysaccharide, although a protective threshold was achieved [14]. Similarly, another RCT among teenagers reported that the immune response to MenC, Y and W polysaccharide was lower with sequential administration, namely when diphtheria toxoid-adsorbed vaccine (Td) was given a month before MCV4-DT [41]. Another recent trial reported that the proportions of subjects with an adequate immunological response against MenA, C and W was lower when MCV4-TT vaccine was given to a toddlers aged 12–23 months after a previous DTP shot [42]. A trial among Korean military recruits in 2013 has shown that just a three days gap between administration of tetanus-diphtheria toxoids and MCV4-CRM197 resulted in a significant suppression [43]. Conversely, in other trials, both concurrent [44] or prior exposure [45,46] to DTP or its components improved the immune response to both nonvalent C conjugate vaccine and MCV4 among humans and in animal models. For instance, adult mice with previous exposure to TT had shown an enhanced immunogenicity to MenC-TT [46].

This degree of inconsistency was much less seen when analysing immune responses to PCV13-CRM197 in both our studies in

Table 1

<table>
<thead>
<tr>
<th>Group A (n = 35)</th>
<th>Group B (n = 35)</th>
<th>Group C (n = 37)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rSBA GMT (95% CI)</td>
<td>404 (172–949)</td>
<td>984 (419–2313)</td>
<td>1235 (538–2835)</td>
</tr>
<tr>
<td>Seroresponse, n (%)</td>
<td>29 (82.9%)</td>
<td>31 (88.6%)</td>
<td>30 (81.1%)</td>
</tr>
<tr>
<td>Seropositive, n (%)</td>
<td>29 (82.9%)</td>
<td>33 (94.3%)</td>
<td>32 (86.5%)</td>
</tr>
</tbody>
</table>

Group A: Tdap before MCV4-CRM197 and PCV13-CRM197; Group B: Tdap with MCV4-CRM197 and PCV13-CRM197; Group C: MCV4-CRM197 and PCV13-CRM197; before Tdap.

GMT: Geometric mean titre; MCV4: quadrivalent meningococcal-CRM197 conjugate vaccine; PCV13: 13-valent pneumococcal-CRM197 conjugate vaccine; Tdap: combined tetanus, reduced diphtheria and acellular pertussis vaccine.

* ANOVA test.

* Chi-square test.
which prior receipt of Tdap in adults had significantly reduced the antibody response to six [32] and to seven [33] of the 13 antigens present in PCV13-CRM197. This consistent finding may be explained by the fact that the pneumococcal vaccine used (PCV13-CRM197) was not changed in both trials. Alternatively, this may demonstrate that polysaccharide components (pneumococcal vs. meningococcal) of the conjugate vaccine themselves could act differently even when both conjugated to the same carrier proteins.

Carrier induced epitopic suppression (CIES) together with carrier priming may explain this inconsistency of the results. Carrier priming refers to the enhanced immune response to the polysaccharide component of the conjugate vaccine in individuals with previous priming with, or exposure to, the carrier protein. The greater secondary immune response could result from pre-existence of anti-carrier immunity (increased memory cells to carrier protein) obtained from earlier exposure [47]. Individuals with pre-existing immunity to the carrier protein may however develop reduced immune response as a result of CIES. CIES refers to the interference with the antibody response to a polysaccharide conjugated to a carrier protein, in individuals previously primed with that particular carrier protein, resulting in a reduction in the immune response to the capsular polysaccharide and an elevated response to the carrier [48]. In general, apart from interference between diphtheria-tetanus containing vaccines and the carrier protein component of the polysaccharide conjugated vaccines, the literature reveals the presence of interaction between the carrier proteins themselves and the findings were contradictory and hard to predict [42].

Coadministration of meningococcal vaccines with vaccines other than Tdap has also been studied. For instance, in a phase 3b randomised trial, the proportions of seroprotective participants (achieving hSBA titers >8) for MenACWY was similar one month after MCV4-CRM197 vaccination alone or in combination with hepatitis A and B vaccines [49]. Similarly, the immune responses to MenACWY one month after MCV4-CRM197 vaccination alone or combined with typhoid and yellow fever vaccines, were similar [50].

The small sample size is a key limitation of this study and an increased number of participants could offer a better demonstration of the effect. The long duration between sampling and testing is yet another limitation. Coadministration of another conjugate vaccine (PCV13-CRM197) has limited the ability to relate the observed effect solely to Tdap, and further head to head analysis is suggested.

Multiple vaccine administration on a single occasion reduces clinic visits, and thus decreases cost and may enhance compliance. Nevertheless, some practitioners favour separate administration to avoid possible interactions or exaggerated adverse events. Travellers such as Hajj pilgrims are usually required to receive more than one vaccine in a short period of time. There is no apparent evidence against giving MCV4-CRM197 or MCV4-TT with Tdap in a single visit to achieve better compliance. However, if separation is required (e.g. when adverse events are suspected) this study showed no difference whether the conjugated vaccines (MCV4/PCV13) were given before or after the antigen containing vaccine (Tdap).

Recent recommendations prefer the conjugate vaccine for pilgrims over its plain polysaccharide rival. Over the past two years, the MCV4 vaccine has completely replaced the polysaccharide in Australia. Being not funded for pilgrims by governments in most developed countries cost as a concern will rise, as MCV4 is significantly more expensive than plain polysaccharide. However, knowing that both (TT and CRM197-conjugated vaccine) can be safely administered with PCV-CRM197 and Tdap will provide more convenient options to the pilgrims.

This paper concludes reporting on two RCTs with identical design and similar vaccines, but different carrier proteins, conducted in 2014 and 2015. Results of this analysis are consistent with those previously published. Prior exposure to Tdap could suppress the immunological response to PCV13-CRM197 and to MCV4-TT. Our current study with MCV4-CRM197 showed differences in the same direction but not significant. This may be due to lack of power.

5. Conclusion

Based on this study we continue to support concurrent administration of MCV4-CRM197 and Tdap. However, we suggest further investigation into whether carrier induced suppression is a public health issue.

Declaration of Competing Interest

Dr Leon Heron and Professor Robert Booy have received funding from Baxter, CSL/Seqirus, GSK, Merck, Novartis, Pfizer, Roche, Romark and Sanofi Pasteur for the conduct of sponsored research, travel to present at conferences or consultancy work; all funding received is directed to research accounts at The Children's Hospital at Westmead. Dr Harunor Rashid received fees from Pfizer, Novartis and Sanofi Pasteur for consulting or serving on an advisory board. Prof Ray Borrow and Dr Jennifer Louth conduct contract research on behalf of Public Health England for GSK, Pfizer and Sanofi Pasteur. The other authors have declared no conflict of interest in relation to this work.

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Chapter 6: Pattern of Immune Response Over Years Following Vaccination with Meningococcal Serogroup C Conjugate Vaccines

After shedding some light on the issue of immunological interference it is worth considering another important issue with respect to the immune response to MCC: the gradual waning of immune response, particularly following early childhood immunisation. Conjugate vaccines initially show very strong immune responses but immunity wanes over several years [16, 95, 96]. Even though the incidence of IMD has remained low in many countries since the introduction of routine childhood immunisations, this may be explained by the reduction of carriage induced by catch up immunisation campaigns targeting adolescents and young adults. A large number of studies have been published evaluating changes in the immune response to meningococcal conjugate vaccines several years following vaccination in various age groups. Interestingly, waning was not the only observed change; boosting of immune responses has also been noted [97].

This chapter represents a secondary analysis of available data on changes over several years to the immune response to meningococcal serogroup C conjugate vaccines among children vaccinated in early childhood.

What is the context?

- Monovalent meningococcal serogroup C conjugate vaccines are highly immunogenic.
- Immune responses to these vaccines wane as early as one year following early childhood vaccination.
- A recent report highlighted a rise in antibody titers, instead of waning, in some participants.

What is new?

- A secondary analysis of sequential results of meningococcal serogroup C bactericidal antibody titers shows that the phenomenon of a rise in antibody titers in the absence of re-vaccination does occur in a small minority of children.

What is the impact?

- A further investigation is required to explain this phenomenon, but may include ongoing exposure to carried strains of MenC.
- The rise in antibody titers without a booster dose of vaccine may indicate a decline in the level of herd immunity developed during the past decades.
Evidence for Rise in Meningococcal Serogroup C Bactericidal Antibody Titers in the Absence of Booster Vaccination in Previously Vaccinated Children

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Background: The introduction of meningococcal serogroup C (MenC) conjugate vaccines in the United Kingdom and Australia led to an impressive decline in the incidence of invasive disease. This study examined bactericidal antibody titers over time in the UK and Australian children who received a MenC conjugate vaccine in early childhood to test the hypothesis that ongoing boosting of immunity in the absence of further doses of vaccine in some children may contribute to ongoing protection from disease.

Methods: Serum bactericidal assay using rabbit complement (rSBA) titers at each follow-up visit were compared with all preceding visits to identify any ≥4-fold rise in titers. The proportion of children with a ≥4-fold rise in rSBA titers in paired sera at any visit-to-visit comparison was calculated.

Results: Of 392 children with at least one set of paired sera in the Australian cohort, 72 (18.4%) had a ≥4-fold increase in rSBA titers at least one year after vaccination, including six children (1.5%) who showed evidence of boosting twice. Of 234 children with at least one set of paired sera in the UK cohort, 39 (16.7%) had a ≥4-fold rise in rSBA titers at least one year after vaccination including 2 children (0.9%) with evidence of boosting twice.

Conclusions: A substantial minority of children immunized with MenC conjugate vaccine in early childhood had a rise in bactericidal antibody titers in the years after immunization in the absence of booster vaccination. This occurs most commonly at around 6–7 years of age corresponding to school entry and greater social mixing and might indicate exposure to MenC carriage.

Key Words: bactericidal antibody titer, meningococcal serogroup C conjugate vaccine, natural boosting, Neisseria meningitidis, rabbit complement serum bactericidal assay

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Despite this, the incidence of invasive MenC disease has remained low for more than 10 years after the introduction of MCC vaccines. In addition to the effect of ongoing herd immunity from previous immunization of older children and adolescents, this may in part be caused by ongoing boosting of immunity in at least some children through exposure to meningococci (through carriage) or other bacterial species (cross-reactive antibodies), resulting in a rise in MenC bactericidal antibody titers over time in the absence of booster doses of vaccine. This study aimed to test this hypothesis by examining rSBA titers over a period of postvaccination follow-up in the UK and Australian children who received an MCC vaccine in early childhood.

**MATERIALS AND METHODS**

**Study Design**

The analysis for this study examined data that were collected as part of studies conducted in Australia and the United Kingdom between 2001 and 2010 involving children 12 to 48 months of age at the time of MCC vaccination.

The design of the Australian study has been described previously. Briefly, an open-label, randomized-controlled, multicenter trial was conducted in which children 12 to 18 months of age, previously primed with *Haemophilus influenzae* type b vaccine but no MenC vaccine as part of routine infant immunizations, were randomized (3:1) to receive either one dose of a combined *Haemophilus influenzae* type b and MenC-TT conjugate vaccine (Mentorix, GlaxoSmithKline Biologicals [GSK], Brentford, United Kingdom) or separate *Haemophilus influenzae* type b-TT vaccine (Hiberix, GSK Biologicals) and MenC vaccine conjugated to Cross-Reactive-Material-197 (CRM197) (Meningitec, Wyeth/Pfizer Vaccines, Pearl River, NY). Children were followed up for 5 years, and 7 blood samples were collected including pre-MCC and 1 month post-MCC vaccination and then on a yearly basis for 5 years. The study was conducted between 2006 and 2012. rSBA titers were measured at either GSK Biologicals central laboratory in Rixensart, Belgium, or at the Health Protection Agency (HPA) reference laboratory in Manchester, United Kingdom.

Data from the United Kingdom were drawn from an observational study conducted by the Oxford Vaccine Group in which children who had received a single dose of a licensed MCC vaccine as toddlers (between 13 and 45 months, median 21 months of age) had blood samples taken over 10 years between 2001 and 2010. The majority of vaccinations occurred as part of the national catch-up immunization campaign in 1999 to 2000, while 4/287 children were vaccinated between February 2001 and March 2002. Most children (259/287) had received a dose of MenC-CRM197 vaccine (Meningitec, Wyeth/Pfizer Vaccines), whereas the specific vaccine received could not be determined for 36 children. rSBA analysis was undertaken on these blood samples at the HPA reference laboratory, Manchester, United Kingdom.

**Data Analysis**

Original data from both studies were obtained from the lead authors. A visit-to-visit comparison was done in which rSBA results at each visit were compared with all preceding visits (when performed at the same laboratory in the Australian cohort) to identify the occurrence of a ≥4-fold rise in titers (prevacccination sera were not included in the analysis). Children with missing results were excluded from the analysis at that particular visit-to-visit comparison only. A second episode of ≥4-fold rise in rSBA titers for an individual participant was only included if the episodes were separated by a period of waning in antibody titers. The proportion of children with a ≥4-fold rise in rSBA titers in paired sera at any visit-to-visit comparison was calculated using the total number of paired sera, with results available for analysis as the denominator for each comparison. Secondary analysis aimed to identify the proportion of children with ≥4-fold rise at each particular visit. For this analysis, only children with results available for a particular visit, and at least one earlier visit (from the same laboratory in the Australian cohort), were included and used as the denominator for each visit. Children with evidence of boosting in rSBA titers were grouped according to time (visit/age) at which this occurred. Mean age and range of ages at each visit were calculated for all children included in the analysis at that time point. In case of unavailability of raw data, the mean age and range of ages of the total cohort of children enrolled at that time point were used. Where data were available (for the Australian cohort only), the relationship between initial (1 month postvaccination) responses and evidence of subsequent boosting was also explored. No comparisons were made between results of assays performed at different laboratories.

**RESULTS**

**Australian Cohort**

rSBA titers results from the second- and third-year visits were only available from the GSK laboratory, while the results of the fourth- and fifth-year visits were only available from the HPA laboratory. Results from blood drawn 1 month and 1 year postvaccination were available from both laboratories.

Out of 433 children in the total cohort, 392 children had at least one set of comparable paired sera (ie, from the same laboratory) available for analysis. Of those, 72 children (18.4%) had a ≥4-fold rise in rSBA titers at least once at any time point after vaccination, including 6 children (1.5%) who had a ≥4-fold rise in rSBA titers occurring within the 5-year follow-up, that is, rSBA titers were high after vaccination, waned and subsequently boosted before waning and boosting again. Boosting seemed to occur most frequently between 2 and 3 years after vaccination (Table 1), as evidenced by the highest proportion of boosters identified (27 out of 291 [9.3%] children with paired samples) when blood drawn at 3 years postvaccination (mean age 48.5 months) was compared with the 2-year postvaccination visit (mean age 36.6 months). A slightly lower number (7.9%) also showed evidence of boosting later on between 4 and 5 years postvaccination.

In the Australian cohort, results available from both laboratories showed that nonboosters have higher initial (1 month postvaccination) antibody responses compared with those who later boosted, with geometric mean titers (GMTs) of 179.0 (215–362) versus 190 (115–313) and 515 (452–586) versus 404 (301–543) from HPA and GSK laboratories, respectively. Furthermore, irrespective of age or time since vaccination, there were 29 and 49 episodes where a ≥4-fold rise in rSBA titers was identified based on results from HPA and GSK laboratories, respectively. rSBA GMTs of blood drawn in the visit immediately before the boost were 5.59 and 9.82, with rSBA titers of <1:8 (lowest limit of detection) in 25/29 (86%) children and 49/49 (100%) with rSBA titers <1:8 in the visit immediately before the boost were 5.59 and 9.82, with rSBA titers of <1:8 (lowest limit of detection) in 25/29 (86%) children and 49/49 (100%) with rSBA titers <1:8 (lowest limit of detection) in 25/29 (86%) children and 49/49 (100%) with rSBA titers <1:8 (lowest limit of detection) in 25/29 (86%) children and 49/49 (100%) with rSBA titers <1:8 (lowest limit of detection) in 25/29 (86%) children and 49/49 (100%) with rSBA titers <1:8 (lowest limit of detection) in 25/29 (86%) children and 49/49 (100%) with rSBA titers <1:8 (lowest limit of detection) in 25/29 (86%) children and 49/49 (100%) with rSBA titers <1:8 (lowest limit of detection) in 25/29 (86%) children and 49/49 (100%) with rSBA titers <1:8 (lowest limit of detection) in 25/29 (86%) children and 49/49 (100%) with rSBA titers <1:8 (lowest limit of detection) in 25/29 (86%) children and 49/49 (100%) with rSBA titers <1:8 (lowest limit of detection) in 25/29 (86%).

**UK Cohort**

Of 300 children in the total cohort, 234 had at least one set of paired sera available for analysis. Thirty-nine children (16.7%) had a ≥4-fold rise in rSBA titers at least once at any time point after vaccination including 2 children (0.9%) who had a ≥4-fold rise in rSBA titers occurring twice during the 10-year follow-up period. The results for children from the United Kingdom are outlined in...
TABLE 1. Number of Children With ≥4-Fold Rise in rSBA Titers at Any Time Point Since Vaccination—Australian Cohort (Visit-to-Visit Comparison)

<table>
<thead>
<tr>
<th>Visit-to-Visit Comparison*</th>
<th>Number of Children With Paired Blood Samples</th>
<th>Mean Age and/or Range of Ages at Blood Draws, in Months†</th>
<th>Number (%) of Children With ≥4-Fold Rise in rSBA Titers</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Y vs. 1 M§</td>
<td>341</td>
<td>13–19, 24.6</td>
<td>4 (1.2%)</td>
<td>Based on results from GSK laboratory</td>
</tr>
<tr>
<td>1 Y vs. 2 Y§</td>
<td>161</td>
<td>13–19, 24.6</td>
<td>2 (0.6%)</td>
<td>Based on results from HPA laboratory</td>
</tr>
<tr>
<td>2 Y vs. 1 M§</td>
<td>305</td>
<td>24.6, 36.6 (35–40)</td>
<td>27 (9.3%)</td>
<td>All included in comparison above</td>
</tr>
<tr>
<td>2 Y vs. 2 Y§</td>
<td>322</td>
<td>13–19, 36.6 (35–40)</td>
<td>8 (2.8%)</td>
<td>Two not included as no sample available at 2 year</td>
</tr>
<tr>
<td>3 Y vs. 1 M§</td>
<td>306</td>
<td>13–19, 48.5 (47–52)</td>
<td>2 (0.7%)</td>
<td>All included above</td>
</tr>
<tr>
<td>3 Y vs. 2 Y§</td>
<td>145</td>
<td>24.6, 60.6 (59–64)</td>
<td>5 (3.4%)</td>
<td>One not included above as no sample available at 1 year</td>
</tr>
<tr>
<td>4 Y vs. 1 Y‡</td>
<td>176</td>
<td>13–19, 60.6 (59–64)</td>
<td>1 (0.6%)</td>
<td>Six boosted for 2nd time</td>
</tr>
<tr>
<td>4 Y vs. 1 M§</td>
<td>176</td>
<td>13–19, 60.6 (59–64)</td>
<td>8 (5.7%)</td>
<td>All included above</td>
</tr>
<tr>
<td>5 Y vs. 4 Y‡</td>
<td>267</td>
<td>60.6 (59–64), 72.4 (71–77)</td>
<td>21 (7.9%)</td>
<td>All included above</td>
</tr>
<tr>
<td>5 Y vs. 1 Y§</td>
<td>140</td>
<td>24.6, 72.4 (71–77)</td>
<td>3 (1.2%)</td>
<td>All included above</td>
</tr>
<tr>
<td>5 Y vs. 1 M§</td>
<td>168</td>
<td>13–19, 72.4 (71–77)</td>
<td>5 (2.8%)</td>
<td>All included above</td>
</tr>
</tbody>
</table>

*Visit-to-visit comparison—for example, 1 Y vs. 1 M: rSBA titer at 1 year post-vaccination compared with rSBA titer at 1 month post-vaccination.
†The mean and/or range of ages of the total cohort of children enrolled at that time point.
‡Results from GlaxoSmithKline (GSK) Biologicals central laboratory.
§Results from Health Protection Agency reference laboratory.

Table 2. In this cohort, boosting seemed to occur most frequently between 3 and 4–5 years postvaccination as evidenced by the highest proportion of boosters identified (15 out of 125 [12%] children with paired samples) when comparing blood drawn at 4–5 years postvaccination (mean age 84.4 months) compared with the 3-year postvaccination visit (mean age 60.4 months).

Irrespective of age or time since vaccination, there were 35 episodes where a ≥4-fold rise in rSBA titers was identified. rSBA GMT of blood drawn in the visit immediately before the boost was 3.70, with rSBA titers of <1:4 (lowest limit of detection) in 22/35. Conversely, rSBA GMT of blood drawn at the visit when boosting was identified was 48.5, with minimum rSBA titers of 1:8 in all samples.

Figure 1 and Table 3 outline the total number and proportion of children with ≥4-fold rise at each particular visit after vaccination for both cohorts.

DISCUSSION

The main findings from both original studies previously published elsewhere demonstrated that the majority of children had waning of rSBA titers over time after vaccination. Investigators reported a substantial (nearly 10-fold) decrease in rSBA GMTs in the Australian cohort from 1 month (621.0 [95% confidence interval: 480.3–802.9]) to 12 months (63.8 [43.3–94.1]) postvaccination. Similarly, results from United Kingdom demonstrated that by 10 years after immunization, only 15% of children had MenC rSBA titers above the threshold for protection (≥1:8). This is in line with results from many studies of MCC vaccine immunogenicity that show initially robust immune responses but waning immunity over several years.

MCC vaccines are highly immunogenic in young children, with at least 91% and up to 100% of children developing MenC rSBA titers ≥1:8 one month after immunization at age of 12–18
months. The introduction of MCC vaccines has proved to be very effective in both the United Kingdom and Australia in controlling invasive disease, with disease incidence reduced to near zero. In addition, MCC vaccines reduced carriage of the epidemic serogroup C ST-11 complex meningococci by around 80% over the first 2 years in the United Kingdom. This study demonstrates that although immune responses were not maintained by the majority of children, a substantial minority show evidence of boosting of antibody titers without additional doses of vaccine. A $\geq 4$-fold rise in rSBA titers between 1 month and 10 years after vaccination was seen in 18.4% and 16.7% of children in Australian and the UK cohorts, respectively.

In both studies, children received a single dose of a licensed MCC vaccine as toddlers; however, the children in the UK cohort were slightly older at the time of vaccination, and this difference persisted to later blood draws, which may explain the slightly different results between the 2 cohorts. We are unable to exclude similar patterns between the 2 cohorts in “peaks” in the proportion of children with a rise in their rSBA titers because intervals between vaccination and blood draws were different between the 2 cohorts, and data from the Australian cohort did not include follow-up beyond 5 years postvaccination and data from the United Kingdom did not include rSBA titers from the first 2 years postvaccination.

From the date ranges for which we have data, a $\geq 4$-fold rise in rSBA titers occurred most commonly at around 4–5 years postvaccination in the UK cohort when children were around 7 years of age and at around 3 years postvaccination in the Australian cohort when children were around 4 years of age, with a second smaller peak in the proportion of “boosters” occurring around 5 years postvaccination when children were around 6 years of age. The lower percentage of children who showed evidence of boosting 4 years postvaccination in the Australian cohort may be related to the longer time interval between compared blood draws for this time point. One year time intervals were compared between 1 and 2 years, 2 and 3 years and 4 and 5 years postvaccination; however, because of the unavailability of paired blood results from the same laboratory between 3 and 4 years postvaccination, comparisons could only be made between 1 and 4 years or 1 month and 4 years postvaccination for this time point. The high proportion of children with rSBA rise of $\geq 4$-fold at visits between the mean ages of 48.5 to 85 months in both cohorts may be caused by increased social mixing as a result of daycare, preschool and school entry at these ages.

This natural boosting in rSBA titers may occur for several reasons, including exposure to carried MenC or to cross-reactive antigens, as well as host genetic differences or may simply be caused by stochastic changes. MenC is known to asymptptomatically colonize the upper airways of individuals, and mucosal colonization with meningococci is typically an immunizing event, causing as a result of daycare, preschool and school entry at these ages.

This and Any Prior Visit

<table>
<thead>
<tr>
<th>Time Since Vaccination</th>
<th>Number of Children With Samples at This and Any Prior Visit</th>
<th>Mean Age (±Range) at Blood Draws, in Months</th>
<th>Number (%) of Children With ≥4-Fold Rise in rSBA Titers Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australian cohort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>341</td>
<td>24.6 (35–40)</td>
<td>18 (5.4%)</td>
</tr>
<tr>
<td>2 years</td>
<td>334</td>
<td>48.5 (47–52)</td>
<td>29 (9.1%)</td>
</tr>
<tr>
<td>3 years</td>
<td>319</td>
<td>60.6 (59–64)</td>
<td>6 (3.4%)</td>
</tr>
<tr>
<td>4 years</td>
<td>177</td>
<td>72.4 (71–77)</td>
<td>21 (7.9%)</td>
</tr>
<tr>
<td>5 years</td>
<td>268</td>
<td>72.4 (71–77)</td>
<td>21 (7.9%)</td>
</tr>
<tr>
<td>United Kingdom cohort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 years</td>
<td>193</td>
<td>60.7 (54–73)</td>
<td>6 (3.1%)</td>
</tr>
<tr>
<td>4–5 years</td>
<td>151</td>
<td>85.0 (73–99)</td>
<td>19 (12.6%)</td>
</tr>
<tr>
<td>7 years</td>
<td>158</td>
<td>108.6 (103–122)</td>
<td>10 (7.2%)</td>
</tr>
<tr>
<td>10 years</td>
<td>98</td>
<td>147 (138–162)</td>
<td>6 (6.1%)</td>
</tr>
</tbody>
</table>

**FIGURE 1.** Proportion of children with a ≥4-fold rise in rSBA titers at each particular visit.

### TABLE 3. Number of Children With a ≥4-Fold Rise in rSBA Titers at Each Specific Visit: Both Australian and UK Cohorts
susceptible to acquisition of MenC that is not adequately identified in cross-sectional carriage studies. This could mean that ongoing herd immunity may not be well-maintained in the long-term and supports the recent decision by the UK Joint Committee on Vaccination and Immunisation to introduce an adolescent booster dose of MCC vaccine in 2013 (subsequently replaced with a tetravalent MenACWY conjugate vaccine since 2015). Other potential factors associated with an increase in the carriage rate of MenC that may contribute to this rise in rSBA titers, such as exposure to smokers, crowded living conditions or presence of adolescents in the same household, could not be investigated in these cohorts because of the retrospective nature of the analysis. Exposure to other carried organisms or other meningococci (cross-reactive antigens) is theoretically possible; however, to our knowledge, this has not been definitively demonstrated to produce bactericidal antibody responses.

Alternatively, there may be subtle differences in the immune responses of different individuals that determine the rapidity of waning of antibody or a potential for a rise in antibody titers. The initial antibody response to vaccination may provide a clue to these host genetic differences. It is possible that children who had a better initial antibody response “used up” most of their pool of B cells to become antibody-secreting cells and, therefore, were less likely to boost as well subsequently in response to further stimulation, that is, a greater proportion of B cells differentiated into plasma cells at the expense of priming memory B cells. A similar phenomenon has been noted previously with children who had an initial greater bactericidal antibody response to primary MCC vaccines, having lower postbooster antibody responses.  

Four children showed a delayed response to vaccination with a ≥4-fold rise in rSBA titers between 1 month and 1 year after immunization. This may be early evidence of boosting or may simply be evidence of a slow response to vaccination. The peak antibody response is thought to occur between 4 and 6 weeks after immunization; however, there is evidence that the germinal center reaction after vaccination may continue longer than expected with B cells maturing and differentiating for a longer time. MenC-specific memory B cells have been shown to increase between 5 months and 1 year after primary vaccines in the absence of booster vaccine doses, which may also explain the rise in antibody titers in a small number of children in this study within the first 1–2 years after vaccination.

In conclusion, a substantial minority of children immunized with MCC vaccine in early childhood had a rise in bactericidal antibody titers in the years after immunization in the absence of booster vaccine doses. This raises interesting questions about host genetic variability in initial and ongoing immune responses to vaccines with evidence that a greater initial immune response may result in a lower likelihood of subsequent boosting (and therefore persistence) of the antibody response. Interestingly, the age at which most of these children showed evidence of boosting occurs most commonly at around 6 or 7 years of age corresponding to school entry and greater social mixing. This may be evidence of exposure to carriage of MenC. Along with the known waning of immunity in the majority of immunized children, this may lead to a resurgence in disease rates, and though this has not yet been observed, this phenomenon raises some concern for maintenance of herd immunity, particularly in Australia where there is currently no adolescent MCC vaccine booster on the national immunization schedule.

**ACKNOWLEDGMENTS**

We thank the Oxford Vaccine Group for providing access to the raw data for the UK cohort and Dr S. DiNatale and Dr Andrea McCracken from GlaxoSmithKline for providing data for the Australian cohort. We also thank the children and families who participated in both original studies from which these data are drawn.

**REFERENCES**


SECTION D: SUMMARY AND CONCLUSION

Summary

This is the summary of my thesis’s key findings. Since each individual publication/chapter has already been discussed elaborately, this section only provides a bullet-point list of findings (Figure 2):

My systematic reviews showed:

- Despite advancements in vaccination policies and methodologies, IMD remains a public health concern and sporadic cases and outbreaks continue to occur.

- The disease affects all age groups but predominantly affects infants, adolescents and young adults, with certain populations and settings that share some characteristic such as over-crowdedness, intense congestion and prolonged close contacts being more vulnerable to the disease.

- Outbreaks of IMD commonly occur among travellers (including Hajj pilgrims and refugees), and with closed and semi-closed populations including university freshmen and military recruits.

- Adoption of high risk behaviours such as smoking, bar patronage and intimate kissing further increases the risk of IMD.

- MenC conjugate vaccines, regardless of carrier protein used, are safe, highly immunogenic and provoke immune memory, but the initial high antibody response does not persist long, particularly following early childhood immunisations.

- TT-conjugated MenC vaccines appear to be more efficient at inducing immunologic memory than CRM197-conjugated MenC vaccines, namely Meningitec™.
My original researches showed:

- Vaccine uptake is suboptimal among two key groups within the context of Hajj: domestic pilgrims, and health care workers including trainees.

- Holding a tertiary academic qualification, receipt of pre-Hajj health advice, being employed, or being a traveller to Makkah (either from overseas or within Saudi Arabia but from outside Makkah province) are predictors for better vaccine acceptance among pilgrims.

- The advice of authority on ensuring pre-Hajj vaccination is an important motivator for vaccine uptake. Lack of awareness of pre-Hajj vaccine requirements and shortage of time are the main declared barriers among pilgrims and HCWs at Hajj.

- Pre- and post-Hajj carriage of meningococci was almost non-existent during the Hajj seasons of 2017 and 2018 among a sample consisting of mostly domestic pilgrims.

- In the same sample, pneumococcal carriage was surprisingly high (50/223, 22.4%) 10-11 months following the Hajj.

- Concurrent or sequential administration of MenACWY-CRM197 and diphtheria–tetanus containing vaccine showed no effect on immune response to MenW; nevertheless, caution should be exercised in interpreting and generalising these results as the study lacks power.

- A substantial minority of children developed a ≥4-fold rise in serum bactericidal assay using rabbit complement (rSBA) titers 1-10 years following early childhood vaccination with a meningococcal serogroup C conjugate vaccine without receiving a booster dose.
Carriage of meningococci was almost non-existent in 2016/17.

Rates of pneumococcal carriage was surprisingly high (~20%).

Vaccine uptake among domestic pilgrims and HCWs is suboptimal.

Sex, education, employment, pre-Hajj health advice and travel distance are important influencing factors.

Vaccine Uptake

MCC Immunology

- MCCs are safe, immunogenic and induce immune memory.
- The initial response does not persist long.
- MCC-TT appears to be more immunogenic than MCC-CRM$_{197}$.

Immunology

- IMD is a public health concern.
- Crowded settings are more vulnerable to IMD.
- Behaviours such as smoking and intimate kissing raises the risk further.

Systematic reviews

- Substantial minority of children had a rise in SBA titres years following vaccination without a booster dose.

Immune Persistence

- Concurrent or sequential administration of Tdap and MenACWY-CRM$_{197}$ has not shown any effect on MenW immune response.

Immune interaction

- Carriage of meningococci was almost non-existent in 2016/17.
- Rates of pneumococcal carriage was surprisingly high (~20%).

Carriage in the Hajj

Legend

CRM$_{197}$, Diphtheria cross-reactive material; HCWs, Healthcare workers; IMD, Invasive meningococcal disease; MCC, Meningococcal serogroup C conjugate vaccine; MenACWY-CRM$_{197}$, meningococcal serogroups A, C, W and Y CRM$_{197}$ conjugate vaccine; MenW, *Neisseria meningitidis* serogroup W; SBA, Serum bactericidal assay; TT, Tetanus toxoid.
Limitations

This section highlights major limitations of the studies included in this thesis or those that are directly related to the overall conclusion of the thesis.

Recall bias is a concern with regard to the cross-sectional surveys; also the inability to determine the exact date of vaccination, differentiate receipt of polysaccharide vaccine from conjugate vaccine or establish a true cause and effect relationship are limitations. Additionally, the relatively small sample sizes, mainly of the immune interference trial, as well as the vaccine uptake surveys, are yet another drawback of this thesis.

Failure to achieve the required sample size for the meningococcal carriage RCT, due to resource constraints and logistic issues, and a subsequent large proportion of participants who missed the follow up visits are the most important limitations. Additionally, obtaining oropharyngeal rather than nasopharyngeal swabs is another limitation, that could be responsible for missing some carriage, as the meningococcus primarily colonises the nasopharynx. Furthermore, comparing the findings of this trial with others conducted during different seasons and mainly among international pilgrims; the generalisability and interpretation of the findings are limited by the absence of previous trials among domestic pilgrims whose Hajj journey is very different to that of international pilgrims in many aspects.

The near zero meningococcal carriage detected in this trial also impeded our ability to investigate the primary objective of the trial, and the question of whether the conjugate vaccine is better than the polysaccharide vaccine in reducing pharyngeal carriage of meningococci remains unanswered.
Regarding the analysis of the children’s rSBA titers over time, investigation of the reasons behind the rise in titers in some children was not possible due to limited data on their clinical status during the course of the study e.g. carriage status, history of medical illness or travel.
Conclusion

The conclusions and outcomes of this thesis have been schematically summarised in Figure 3. Briefly, the early 1990s saw a global increase in the case incidence and outbreaks of IMD, which continued to be concentrated in epidemic regions and among certain populations: children, closed and semi-closed populations, attendees of mass gatherings and travellers. Widespread use of polysaccharide meningococcal vaccines and subsequent switch to the use of more immunogenic conjugate vaccines covering more serogroups (four) have led to a dramatic decline in both the incidence and prevalence of disease. However, IMD remains uncontrolled globally, and sporadic cases and outbreaks continue to occur.

The hope always is to improve the current situation by reducing the burden to a minimum, or even to completely eradicate the disease. However, there are several outstanding issues, such the waning of immune responses following vaccination, particularly in young children, which may lead to resurgence in the disease in the future if not closely monitored. Accordingly, this thesis has addressed certain aspects that may improve the current status of control and also focused on issues that may negatively impact the current status.

The Hajj, as an annual event, involves travellers from all over the world who live in overcrowded and confined areas, and represents an exceptional case for this thesis to explore the pertinent issues in meningococcal carriage, disease and vaccination. Moreover, the current strict vaccination policy enforced by the Saudi Arabian government provides the opportunity to explore several important issues regarding meningococcal vaccination, including (a) vaccine coverage, (b) concerns regarding immune interference, especially with the widespread use of conjugate vaccines and (c) the effect of vaccination on pharyngeal carriage of meningococci.
There have been no Hajj-related outbreaks of IMD since 2002 and various reports have demonstrated satisfactory vaccination coverage among pilgrims; however, the only report focusing on domestic pilgrims, a key group attending Hajj, indicates a low vaccine coverage and the data are outdated. This thesis confirms this fact and demonstrates a suboptimal vaccination rate among domestic pilgrims and also among HCWs deployed at Hajj. Despite the limited sample size, both surveys provide a snapshot indication of meningococcal vaccine coverage among these important, but under-studied groups. They also identify for the first time some predictors, facilitators and barriers towards vaccine uptake. Predictors such as holding a tertiary academic qualification, being employed, receipt of pre-Hajj health advice or being a traveller from outside Makkah province are associated with better vaccination compliance among pilgrims. The Saudi Arabian authorities’ recommendation regarding pre-Hajj vaccination is an important motivator for vaccine uptake. Lack of awareness of pre-Hajj vaccine requirements and shortage of time are the main declared barriers among both groups. Based on these findings, this thesis recommends adoption of measures to increase awareness of the vaccine as a Hajj requirement, and policies to force domestic pilgrims to receive the vaccine in the same way that they are obliged to obtain a Hajj permit before commencing Hajj (in line with the policy for international pilgrims). However, the direct effect of the vaccination policy on the absence of outbreaks of IMD associated with the Hajj is not known yet and hence extensive ethical review should be considered before implementing such a procedure. In its quest to evaluate the Hajj vaccination policy, this thesis attempted to assess the rate of meningococcal carriage in Hajj, particularly among domestic pilgrims. The carriage rate has been noted to be relatively high during Hajj but it varies depending on season, the pilgrim’s country of residence and sampling time. However, there are very few studies on carriage
among domestic pilgrims. In addition to assessing carriage, the study was designed as an RCT aimed to determine if conjugate vaccines are better than their polysaccharides counterparts in reducing meningococcal carriage.

The study encountered several difficulties with respect to providing recommendations regarding the latter aim. Despite being a “negative” trial, the study’s findings were “positive” with respect to the health of participants with the oropharyngeal carriage rate of meningococcus before or after Hajj being close to zero. This may be reassuring but such a finding should be interpreted with caution especially in light of the low vaccination rates among this group. The opportunity to conduct a study during Hajj to determine the ability of conjugate vaccines to reduce meningococcal carriage remains. It is worth mentioning that the study found a relatively high pharyngeal carriage of *S. pneumoniae* and hence we recommend further investigation to evaluate the consequences of this on pilgrims and travellers.

The high discrepancies between the finding of this thesis compared to previous studies, namely on vaccine uptake and pharyngeal carriage, could be due to the fact that overseas pilgrims have been the primary focus of attention in regard to Hajj meningococcal studies in recent years. This highlights the need to address the situation among domestic Hajj attendees (pilgrims and workers) since, apart from their different Hajj experience, they form nearly half of the Hajj population.

Finally, this thesis addressed children as an additional vulnerable population. Successive studies have indicated rapid waning of the immune response following primary conjugate vaccine doses, especially in infants and young children. Despite this, the incidence of disease remains low; although this relatively stable situation could be deceptive. A distinct phenomenon of a rise in bactericidal antibody titers in about 15% of children, instead of
wanning, has been observed by some researchers and this has attracted attention and led to further exploration. This thesis found evidence for a ≥4-fold increase in the rSBA titers in a substantial minority of both UK and Australian children over time after priming with MenC conjugate vaccines in early childhood, in the absence of a booster dose. One potential explanation for this finding, that would be important to investigate further, may be ongoing exposure to carriage of MenC, suggesting that the herd immunity achieved subsequent to the catch up campaigns following introduction of MenC conjugate vaccines into national immunisation programmes is not as well-maintained as health authorities would hope.
Suboptimal vaccination converge among Hajj pilgrims and HCWs at Hajj

Vigorous multilevel awareness campaigns followed by stringent measures may be required

Recall bias, inability to precisely state adherence to policy i.e. type and year of vaccination

A large scale survey to accurately assess adherence and more importantly the predictors and barriers

Near zero meningococcal carriage

A successful vaccination policy or, more likely, a low season of meningococcal carriage

Mostly among domestic pilgrims (who usually have specific characteristics in regard to Hajj experience)

Adequately powered trial in other endemic settings

No effect on MenW when Tdap was given prior to, concurrent with or after MenACWY-CRM$_{197}$

Co-administration is both immunogenic and practical

CIES could not be ruled out due to lack of power

Adequately powered trial to further investigate effects from carrier proteins and their doses is needed

Substantial minority of children with a rise in SBA titers in absence of a booster dose of vaccine

Potential carriage-induced booster response

No record on participants’ carriage status or their conditions during the course of the trial e.g. medical or travel history

Follow up studies to evaluate carriage of *N. meningitidis* as the reason for this rise

CIES, Diphtheria cross-reactive material; MenACWY-CRM$_{197}$, Quadrivalent meningococcal serogroups A, C, W and Y CRM$_{197}$ conjugate vaccine; MenW, *Neisseria meningitidis* serogroup W; SBA, Serum bactericidal assay.
The way forward

The annual Hajj remains an exceptional circumstance in which to investigate communicable diseases, including IMD and others.

A step forward to answer outstanding questions could be large scale studies to investigate meningococcal vaccine coverage among domestic pilgrims, focusing on realistic barriers that impede acceptance of the policy, and taking into account adherence to the policy in terms of the type of vaccine received and the time window of vaccination i.e. at least 10 days before Hajj and at most 3 or 5 years for the polysaccharide and conjugate vaccines respectively. More accurate results could be achieved by matching the records of Hajj vaccination campaigns with the total number of domestic pilgrims disclosed by the responsible authority following each Hajj season.

It may be feasible, in order to practically improve vaccine uptake, to establish an automated process that links both systems, i.e. issuance of Hajj permits and vaccination records, so that the permit is not granted unless the vaccination record confirms receipt of the meningococcal vaccine.

However, since the Hajj policy is based on hypothetical assumptions that have never been investigated with rigorous, large-scale RCTs, future researchers may wish to investigate the bio-ethical ramifications of an enforced vaccination policy for all pilgrims. Additionally, large-scale studies may be required to look at the post-policy efficacy data similar to post-licensure efficacy data analysis that have been performed to understand the real-world impact of MenC conjugate vaccines after they were introduced into various NIPs based only on immunogenicity data.
As for the evaluation of meningococcal carriage and the vaccines’ ability to reduce it, future trials could be improved by including an adjustment of the sample size based on any current data on carriage, and methodological measures to overcome the high rate of missed follow up visits and the ability to obtain swabs immediately after the Hajj. This may include securing the vaccines for the purpose of the study several months prior to the start of recruitment, inviting participants initially to enrol in the study, prior to, and not at the time of vaccination and ensuring their commitment before recruitment, as the current experience proved that catching participants at public health centres while attending to receive their vaccine dose is not feasible. Other ways include accounting for the high proportion of loss to follow up during the sample size calculation or recruiting a larger proportion of international pilgrims as reports suggested a higher carriage rate among them. Carrying out PCR testing alongside conventional culture for all of the swabs at all timepoints would improve sensitivity, and sophisticated laboratory analyses such as whole genome sequencing of isolated strains could provide additional information about currently circulating serogroups and strains globally given the highly diverse community of Hajj.

The Hajj is a feasible setting in which to compare the impact of vaccines on carriage, so the passion is still there to carry out the study again after ensuring logistics and making the changes essential to overcome the limitations, however other endemic settings such as African meningitis belt and outbreak settings may also be used to compare the effect of MenACWY-C and MenACWY-PS vaccines on pharyngeal carriage of meningococci.

The annual Hajj pilgrimage represents a key risk factor for carriage and disease due to its mass congregation, closed and semi-closed settings and involvement of travellers. With the current vaccination requirements set out by the Saudi Arabian government, the Hajj
provides an excellent opportunity to investigate meningococcal carriage, disease and vaccination. Data from well-designed studies set within the context of the Hajj could also be generalisable to other vulnerable populations and settings, at least to a certain extent.

The rise in rSBA titers to levels correlating with possible exposure to the meningococcal antigen in 16% of children - recruited from two countries with blood drawn in different years at various ages - and the occurrence of this rise mainly around the age of school entry with associated increased social mixing should receive particular future emphasis. Further assessments to exclude the possibility of exposure to circulating and colonising meningococci being responsible for this rise through carriage studies among adolescents and young adults or carriage and serology studies among younger children are recommended.

Finally, a future thesis aimed at evaluating various IMD vaccination policies across different vulnerable populations would be a valuable addition to the scientific literature on a disease that remains uncontrolled on a global scale and vaccines that are not routinely available in NIPs except in a limited number of high income countries.
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