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Research Article

Clinical vaccine research on Meningococcal C disease in children in Malta

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Abstract. Clinical vaccine trials in children are extremely important for the investigation of new vaccines as well as for studying different ways of scheduling vaccines that are currently in use. Data from such trials, in addition to epidemiological data on the infectious disease the vaccines are trying to prevent, can be used to introduce vaccines as well as to improve the current immunisation schedules. The purpose of this review is to showcase the clinical vaccine research on meningococcal C vaccines in children that was carried out in Malta in collaboration with the UK from 2010 to 2013, data from which have already been presented and published in peer reviewed journals. This review gives a synopsis of the immunogenicity of reduced dose meningococcal C vaccine schedules in infants as well as the immune kinetics of the antibodies induced following a booster dose at 12 months of age. The practicality of the study findings are discussed, including their relevance to the meningococcal vaccines that were recently introduced on the national immunisation schedule in Malta. Hopefully this research will encourage doctors to show interest in leading future research in children in Malta with appropriate support from our clinical and academic institutions.

Keywords: Clinical Research, RCT, Meningococcal C Vaccines, Paediatrics

1 Introduction

Qualifying and practising as a medical doctor starts to bring up lots of why, what, who, when, where and how questions. Some of these may be addressed by browsing through and critically analysing the medical literature but others may remain unanswered. These unanswered questions lead to the creation of ideas and the formulation of hypotheses that are addressed through research methods. Such questions become even more important when working in Paediatrics. The inherent vulnerability of children and infants provide a challenge to the conduction of clinical trials in children, although Good Clinical Practice (GCP) guidelines which set ethical and scientific standards in research and which are implemented by the EU Clinical trial directive (European Medicines Agency) have made this more feasible. Caring for children with infections, especially those with meningitis and septicaemia that may be fatal or potentially disabling, makes one wonder: considering all the advances in science and technology are we doing enough to control such infections effectively in the 21st century? Clinical practice and research are complimentary in Paediatric Infectious Diseases and provide a holistic approach to children suffering from infections. The importance of research to clinical practice has become ever more recognised during the current SARS-CoV-2 pandemic (World Health Organization, 2020).

One of the major pathogens causing meningitis and septicaemia globally is *Neisseria meningitidis* which mainly affects infants, children below four years of age and adolescents (Centers for Desease Control and Prevention, 2021; European Cetre for Disease Prevention and Control, 2019). Besides endemic disease the meningococcus has the potential to cause epidemics during which older children and adults are also affected (Tyrrell et al., 2002). Despite the rarity of invasive meningococcal disease (IMD) when compared with other childhood infections, such as lower respiratory tract infections and gastroenteritis (World Health Organization, 2021), the meningococcus remains a major public health concern due to the rapidity of disease progression, its potential for causing outbreaks and the associated permanent disabling sequelae that may occur from a very young age.

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2 Epidemiology of meningococcal disease

The meningococcus is classified into 12 different capsular groups based on the biochemical composition of the polysaccharide capsule, with groups A, B, C, W, Y, and more recently X (Delrieu et al., 2011), being responsible for 90% of the global meningococcal disease burden. Capsular groups B and C are the most prevalent groups in Europe and in the US, where capsular group Y is an equally important cause of IMD (Centers for Desease Control and Prevention, 2021; European Cetre for Disease Prevention and Control, 2019). Since the 1950s, the overall mortality from IMD has remained around 8-10% despite advances in intensive care and prompt initiation of appropriate antibiotics (Centers for Desease Control and Prevention, 2021; European Cetre for Disease Prevention and Control, 2019; Sadarangani et al., 2015). Between 7-20% of survivors aged up to 18 years suffer permanent disabilities, including hearing loss, seizures, neurodevelopmental impairment and amputations (Davis et al., 2011; Stein-Zamir et al., 2014). Capsular group C meningococcal disease is associated with a mortality rate of 11-15%, which is higher than the 6-10% case fatality rate for MenB disease (Cohn et al., 2010; Sadarangani et al., 2015; Xu et al., 2012), and with a 10-20% risk of permanent neurodevelopmental and/or physical disabilities (Stoof et al., 2015; Wang et al., 2014). Virulence more likely reflects genomic rather than capsular differences between different strains, with sequence type (ST) 11 meningococci, classically associated with the group C capsule, still behaving more aggressively than other strains even when expressing a different capsular group (Ladhani et al., 2015). A rational and cost-effective strategy for preventing capsular group C disease is through routine childhood vaccination programmes (De Wals et al., 2004; de Soarez et al., 2011; Trotter et al., 2006; Welte et al., 2004).

3 Meningococcal C vaccines

A rise in MenC disease caused by a hyperinvasive ST11 clone led to the development of glycoconjugate MenC vaccines in the 1990s. Glycoconjugate vaccines consist of an oligo/polysaccharide extracted from the capsule of a bacterium which is chemically conjugated to a protein, known as the carrier protein. Three MenC glycoconjugate vaccines were formulated; two having the cross reactive material (CRM197), a non-toxic mutant of diphtheria toxoid, as a carrier protein (Menjugate, GlaxoSmithKline Vaccines, Siena, Italy and Meningitec, withdrawn but previously produced by Nuron Biotech, Schaffhausen, Switzerland) and one utilising tetanus toxoid (NeisVac-C; Pfizer Inc., New York, US). Control of MenC disease has been largely achieved with the introduction of these glycoconjugate vaccines on national immunisation schedules within Europe, with the UK being the first to introduce MenC conjugate vaccination back in 1999 for routine vaccination of infants with a concurrent one time catch-up vaccination of 1-25 year olds (Campbell et al., 2009). The success of these MenC conjugate vaccination programmes was not only a result of direct protection induced by vaccinating infants and toddlers but also a result of decreased transmission induced by catch-up vaccination of adolescents and young adults who are known to have high meningococcal carriage rates reaching up to 25% in 15-19-year-olds (Cartwright et al., 1987) and 32% at 25 years of age (Claus et al., 2005).

Since 1999, the MenC vaccination schedule in the UK was changed three times. The 2, 3 and 4 month MenC infant vaccine priming schedule (priming refers to the initial immune response observed after the first vaccination course) was reduced to a 3 and 4 months schedule with the introduction of a MenC booster dose, incorporated within a combined Haemophilus influenzae type b and MenC tetanus toxoid conjugate vaccine, Hib-MenC-TT, at 12 months of age in 2006 (Campbell et al., 2009). This change followed demonstration of robust immunogenicity with two infant priming MenC conjugate vaccine doses (Richmond et al., 1999) and waning of vaccine effectiveness by 12 months of age (Trotter et al., 2004). Subsequently, the almost complete disappearance of MenC disease in infancy led to reduction of infant priming to a single dose at 3 months of age in 2013 (Public Health England) but with the concurrent introduction of an adolescent boost at 13-14 years of age to maintain adolescent immunity and prevent meningococcal transmission to infants (Pollard et al., 2013). Thereafter the infant MenC dose was removed completely in 2016 since the extremely low rates of infant MenC disease were sustained, although the adolescent MenC dose, as part of the MenACWY conjugate vaccine that had replaced the monovalent MenC conjugate vaccine in 2015 due to an outbreak caused by MenW disease, was retained to maintain herd immunity (Public Health England, 2016).

Reducing the number of infant vaccine doses makes infant vaccination schedules easier to manage due to the ever increasing vaccines that are recommended in this age group. Vaccine schedules with less injections help to increase vaccine uptake by being more attractive to parents. The science behind a change in immunisation schedules comes from clinical vaccine trials designed specifically to address the immunogenicity of reduced dose schedules in conjunction with surveillance of the infectious disease that the vaccines are aimed to prevent. This article will showcase research looking at the prevention of meningococcal

C disease in children that was conducted in Malta and the UK. Data from this research have already been published in peer reviewed journals (Pace et al., 2016; Pace et al., 2015). Dissemination of the findings, which is a result of lots of hard work and long hours invested in conducting the research and which ultimately may have an impact on current practice, is the ultimate goal of any researcher.

4 Clinical research in Malta: A Clinical Vaccine trial

4.1 Study Design

The immune response to reduced dose MenC vaccine schedules was investigated in a Phase IV open label randomised controlled vaccine trial conducted in four sites in the UK, namely Oxford, Bristol, London and Southampton and in one site in Malta (Pace et al., 2015). A clinical vaccine trial site was set up at Mater Dei Hospital, Malta in collaboration with the Oxford Vaccine Group at the University of Oxford. Approvals were obtained from the respective research ethics committees and medicinal regulatory agencies in each country (UK NRES REC No: 10/H0604/7 and Malta HEC No: 24/10). At the time that this study was performed the UK was using 2 infant doses of a MenC conjugate vaccine at 2 and 4 months of age together with a booster dose, as part of the Hib-MenC-TT conjugate vaccine at 12 months of age.

In brief, 509 healthy infants were enrolled when aged between 6-12 weeks and randomised in a 10:10:7:4 ratio into 4 groups as follows: a single infant dose MenC-CRM197 group, a two infant dose MenC-CRM197 group; a single infant dose MenC-TT group and a control group reflecting the number of doses and the formulation of MenC conjugate vaccines given in infancy. The MenC-CRM197 conjugate vaccine formulation was Menjugate (GlaxoSmithKline Vaccines, Siena, Italy) and was given at age 3 months or at 3 and 4 months in the single and two infant dose MenC-CRM197 groups, respectively. NeisVac-C (Pfizer Inc., New York, US) was the MenC-TT formulation given at 3 months of age in the single infant dose MenC-TT group whilst infants in the control group did not receive any MenC vaccine doses in infancy. Following this primary vaccination phase participants proceeded to the booster phase in which the Hib-MenC-TT vaccine (Menitorix, GlaxoSmithKline Biologicals, Rixensart, Belgium) was given at 12-13 months of age. Antibodies against MenC were followed up until 24 months of age. All participants received the other routine vaccinations according to the immunisation schedule in the UK. In the booster phase participants in all groups were vaccinated with the Hib-MenC-TT vaccine at 12 months of age. Blood samples were obtained at 5, 12, 13 and 24 months of age. A subgroup of 64 participants randomly selected from each of the groups had a blood sample six days after the 12 month Hib-MenC-TT vaccine. Following each immunisation participants were observed for 15 minutes for any anaphylactic reactions and parents documented any local or systemic side effects (adverse events) for 5 days later. A MenC serum bactericidal antibody assay, which measures functional antibody, against N.meningitidis C11 (C:16:P1.7-1,1) strain, using baby rabbit complement (MenC-rSBA) was used to measure antibodies against MenC (Pel-Freeze Incorporated, Rodgerson, AZ). In order to assess any statistical significant difference between the standard two dose MenC vaccine schedule and the reduced single dose MenC schedule being studied, a primary objective was set to demonstrate non-inferiority in the MenC rSBA geometric mean titres (GMTs) one month after the 12 month Hib-MenC-TT vaccine. Non-inferiority was met if the lower 95% CI of the difference in the mean log10 MenC rSBA between the single minus the two infant dose MenC-CRM197 groups was >-0.35 (equivalent to a non-inferiority margin of >-10%), An analysis of variance (ANOVA) of the log10 transformed rSBA titres was performed at each blood sampling visit and results presented as GMTs with 95% CIs. A regression model was used to analyse the immune kinetics between the blood sampling visits, including the pre-boost, 6 and 28-day post boost antibody titres (Pace et al., 2016). The aim was to detect a 10% difference between those primed with any MenC conjugate vaccine compared to the unprimed control group. The GMTs, Geometric Mean Fold Rise (GMFR) and Geometric Mean Ratios (GMR) and their 95% Confidence Intervals (CI) were calculated to assess differences in the between the pre-boost and 6 and 28th day post boost antibody titres. For analysis of safety a logistic regression was used to assess binary variables and odds ratios with 95% CI were obtained when comparing two levels of a factor. P values less than 0.05 were considered statistically significant. Immunogenicity analysis was performed using STATA 13 and StatXact 9 whilst SAS v9.3 was used for analysis of safety.

4.2 Results

A total of 509 subjects were recruited with a mean age of 8.5 weeks (Range: 6.9 – 10.6) at enrolment. Gender ratio was balanced, with 51.7% (263) being males and 90.2% were Caucasian.

Following the Hib-MenC-TT boost at 12 months of age participants in the single infant MenC-CRM197 group had MenC rSBA GMTs of 660 [95% CI: 498 to 876] compared to 295 [95% CI: 220 to 398]) in the two infant dose MenC-CRM197 group (figure 1). The difference in

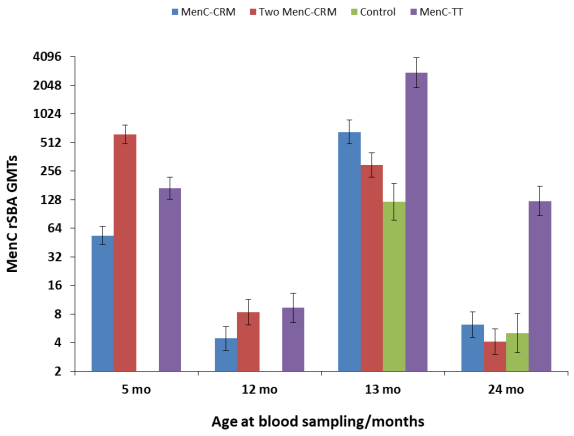

Figure 1: MenC rSBA GMTs measured after the different MenC vaccination schedules (adapted from Pace et al. (2015))

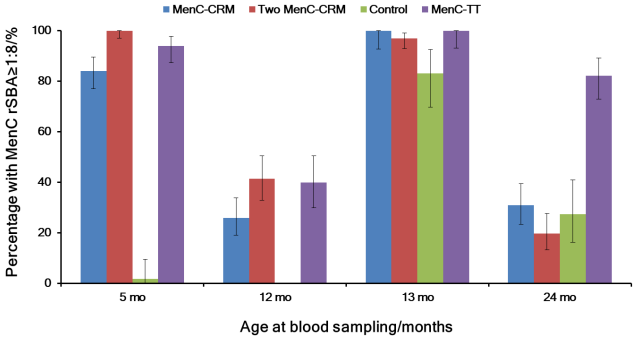

Figure 2: Percentage of participants with a MenC rSBA≥1:8 (error bars indicate 95%CI) (adapted from Pace et al. (2015))

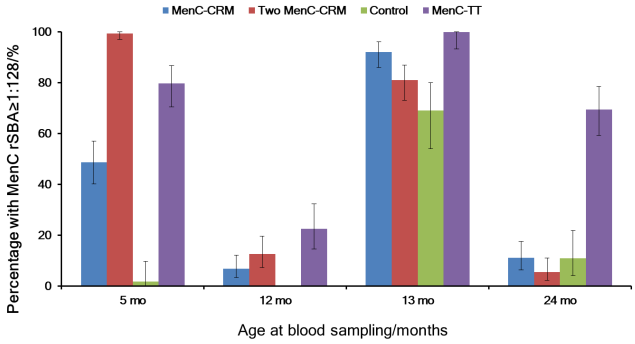

Figure 3: Percentage of participants with a MenC rSBA ≥1:128 (error bars indicate 95%CI) (adapted from Pace et al. (2015))

the mean log10 MenC rSBA between the single and two infant dose MenC-CRM197 Groups was 0.35 (95% CI 0.17 to 0.53) which not only showed that one dose was as good as two MenC-CRM197 doses but that actually a single dose was superior since the 95% CI of the difference did not cross 0 (Pace et al., 2015).

This study revealed differences in the immunogenicity between the MenC vaccine schedules and formulations studied. Two doses of the MenC-CRM197 vaccine in infancy resulted in higher seroprotective rates (taken as MenC rSBA titre of 1:8 or higher with a titre of 1:128 or higher being a more conservative estimate of protection) and GMTs compared to the single dose schedules at 5 months of age (100% vs 84.03%, p≤0.00001 for MenC rSBA≥1:8 and 99.27% vs 48.61%; p≤0.00001 for MenC rSBA ≥1:128 with GMTs: 620.54 vs 53.56; p≤0.00001 when compared to the single dose MenC-CRM197 group and 100% vs 93.94%; p=0.004 with MenC rSBA 4≥41:8; 99.27% vs 79.80%; p≤0.00001 with MenC rSBA≥1:128 and with MenC GMTs of 620.54 vs 169.37; p≤0.00001 when compared to the single dose MenC-TT group (Pace, 2015). By 12 months of age GMTs as well as the proportion of participants with seroprotective titres in all groups had decreased and only 25-41% had MenC rSBA≥1:8 (figure 2) (Pace et al., 2015). Those primed with a single MenC dose had significantly higher GMTs compared to those primed with 2 doses in infancy, one month after the 12 month booster dose (MenC GMTs 660.6 and 2779.2 in the single dose MenC-CRM197 (p=0.0001) and MenC-TT groups (p<0.00001) respectively vs 295.4 in the two dose MenC-CRM197 group) (figure 1) (Pace et al., 2015). One month after the Hib-MenC-TT vaccine boost the proportion of children with rSBA titres ≥1:8 was not significantly different between the Men C primed groups although again those with MenC rSBA titres ≥1:128 were significantly higher after a single MenC priming dose (figures 2 and 3) (Pace et al., 2015).

By 24 months of age the proportion of children with MenC rSBA ≥1:8 declined to <31% in the single or two dose MenC-CRM197 groups and in the control group (figure 2). In contrast the proportion of children with MenC rSBA≥1:8 and ≥1:128 were significantly higher at 82.1% and 69% respectively in those who had been primed with one dose of MenC-TT in infancy and boosted with the Hib-MenC-TT vaccine (p≤0.0001) when compared to the single or two dose MenC-CRM197 groups and the control groups (figure 2) (Pace et al., 2015).

In this study the iantibody dynamics following a conjugate MenC vaccine booster dose as an indicator of immune memory was also studied (Pace et al., 2016) in contrast to previous studies when classically a pure polysaccharide MenC vaccine was used to assess the response to a booster dose several months after the primary vaccination schedule. The practice of boosting with a pure polysaccharide vaccine has raised concerns that even with fractional doses the resultant antibody levels were lower than those induced with primary vaccination, a phenomenon called hyporesponsiveness: this could translate clinically

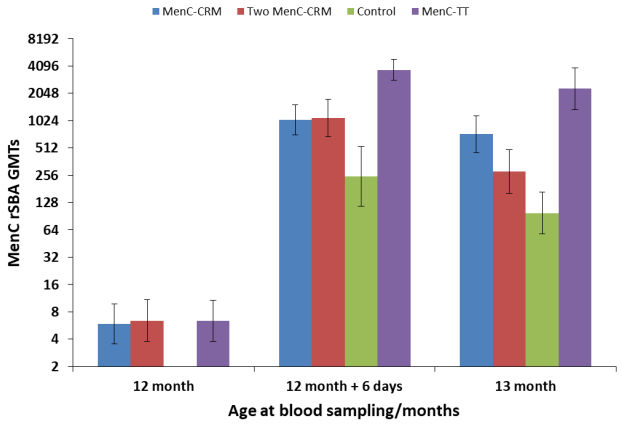

Figure 4: MenC rSBA GMTs at 12 months, 12 months+6 days and at 13 months according to the priming MenC infant schedule (adapted from Pace et al. (2016))

in a lower antibody response when subsequently exposed naturally to the invasive pathogen with possibly an increased risk of infection rather than protection (Gold et al., 1977; MacDonald et al., 1998). Paired sera from the 12 month pre-boost and 6 days post the Hib-MenC-TT vaccine boost were available from 180 participants (Pace et al., 2016). Priming with any MenC vaccine schedule in infancy resulted in significantly higher proportion of participants with MenC rSBA≥1:8 (100% vs 82.6%; p=0.001) and MenC rSBA GMTs (660.6; 295.3, 2779.2 in the single dose MenC-CRM197, two dose MenC-CRM197 and MenC-TT groups, respectively) compared to the control group (MenC rSBA GMTs 121.6; p≤0.00001) (figure 4 (Pace et al., 2016). The GMRs and after adjusting for pre-boost antibodies, the GMFRs, were similarly significantly higher in the primed compared to the unprimed groups (GMRs 4.2, 4.4 and 14.9 for the single dose MenC-CRM197 group, two dose MenC-CRM197 group and the MenC-TT group; GMFRs: 220.2, 229.9 and 778 in the single dose MenC-CRM197 group, two dose MenC-CRM197 group and the MenC-TT group, respectively compared to a GMFR of 57.7 in the control group) (Pace et al., 2016). The proportion of participants with MenC rSBA≥1:8 and ≥1:128 were similar between the MenC-TT and one/two MenC-CRM197 primed groups (100% in all groups with MenC rSBA≥1:8 and for MenC rSBA≥1:128: 100% vs 97.7% and 95.2% respectively), although the GMTs figure 4, GMRs and adjusted GMFRs were significantly higher in those primed with MenC-TT (Pace et al., 2016). No significant differences were seen with the single or two dose MenC-CRM197 primed groups.

An exploratory analysis of the antibody kinetics from the 6th to the 28th day post boost, performed in 162 participants showed a drop in MenC GMTs in all groups figure 4) with the adjusted GMFRs, now expressed as a decline, as well as the adjusted GMRs being significantly less in those unprimed in infancy compared to those who were primed with any of the schedules (Pace et al., 2016). Differences were again noted between those primed with MenC-CRM197 compared to those primed with MenC-TT with the adjusted GMRs being significantly higher following MenC-TT priming (0.48 compared to the single infant dose MenC-CRM197 group; p=0.039 and 0.2 when compared to the two infant dose MenC-CRM197 group; p≤0.0001) (Pace et al., 2016).

4.3 Safety

The most frequent local side effects following the 3 month vaccines were erythema in 45%, induration in 25%, pain in 22% and swelling in 16% reported in any of the groups receiving a MenC conjugate vaccine and with no significant difference seen between the different groups, excluding the control group (Pace et al., 2015). The most frequent systemic side effects were sleepiness and irritability observed in 50% and 66% of infants in each group respectively and again with no significant difference being seen between the groups. Fever ≥38oC was very uncommon and was observed in ≤ 1% of participants in each group (Pace et al., 2015).

Following Hib-MenC-TT vaccination the most frequent local reactions were erythema in 76%, induration in 31%, pain in 29% and swelling in 23% in each group (Pace et al., 2015). The most common systemic side effects were irritability in 61%, drowsiness in 39% and diminished appetite in 35% in each group (Pace et al., 2015). No significant differences were seen between the groups.

4.4 Relevance of the study findings

On an individual level, protection against the meningococcus is critically dependent on having an rSBA GMT ≥1:8 which has to be sustained (Auckland et al., 2006). The reason is that the 24 hour to 7 day incubation period of the meningococcus (De Wals et al., 1981) is shorter than the time needed for the immune system to respond following exposure, which is 9 days for a person who has no detectable MenC antibodies but who has become colonised with the meningococcus (Edwards et al., 1977) and 5-7 days in those who have been vaccine primed and subsequently challenged (Findlow et al., 2011; Snape et al., 2006). Having low MenC rSBA titres would make one potentially susceptible to IMD if exposed (Cano et al., 2004; Trotter et al., 2004). Generating high MenC rSBA GMTs following vaccination is important since it signifies a higher percentage of individuals with MenC rSBA titres ≥1:8. On a population level it is the percentage of individuals with MenC rSBA titres ≥1:8, and more conser-

vatively ≥1:128, that is important in the control of MenC disease (Auckland et al., 2006), the accepted proportion of which depends on the incidence of MenC disease in that same population.

It is a fact that vaccine schedules against meningococcal disease differ between countries with respect to the number of priming doses used in infancy, varying from none to two doses followed by booster doses in early childhood or adolescence (European Centre for Disease Prevention and Control, 2021). This shows that the scientific evidence behind planning of MenC vaccine schedules is not robust enough to result in a standard MenC vaccination programme in all countries where MenC disease is endemic. Immunogenicity data from this randomised controlled trial directly support the reduction of two infant priming MenC doses to one, so long as a booster dose is given around 12-13 months of age. Changes to a vaccination programme would also need to consider the dynamic epidemiology of the disease that is being prevented. Data from this trial support the reduction of infant MenC priming doses from two to one dose, with the retention of the 12 month Hib-MenC boost that was implemented in the UK since 2013 (Public Health England). This was a time when infant MenC disease was low because of the effectiveness of a previous catch up MenC vaccination campaign that led to disease control but with the simultaneous introduction of a MenC conjugate vaccine boost in adolescents, subsequently replaced in 2015 with a MenACWY conjugate vaccine due to a rise in MenW disease in adolescents, to prevent transmission to younger children (Public Health England and National Health Service England, 2015). This study also supports the complete removal of the MenC infant dose adopted in the UK since 2016 since one dose of the Hib-MenC-TT vaccine at 12 months without previous priming also results in robust immunogenicity at 82% with rSBA titres ≥1:8, although such a change was only performed when infant MenC disease was very low due to herd protection which was being sustained through adolescent vaccination. The effectiveness of a MenC vaccination programme adopted in the Netherlands, with a single dose at 14 months of age following control of MenC disease through a catch up campaign of older children and adolescents supported this decision (Kaaijk et al., 2012).

This study also revealed immunogenicity differences induced by different MenC conjugates or by schedules utilising repeated doses of the same MenC glycoconjugate vaccine. Giving two priming doses of MenC-CRM197 in infancy results in a significantly less post boost MenC GMTs after a 12 month Hib-MenC-TT vaccine compared to a single MenC-CRM197 prime and boost schedule. Although not reflected in the number of memory B cells circulating in the blood post MenC vaccination (Khatami et al., 2014), this could be a result of a difference in the amount of B cells induced in lymphoid tissue which may be less when a higher concentration of MenC-CRM197 (by giving more than one dose) is used for priming (Pace et al., 2015).

A single MenC-TT dose at 3 months resulted in significantly higher MenC rSBA GMTs compared to a single MenC-CRM197 dose. In addition the MenC antibodies measured after the 12 month Hib-MenC-TT boost were again significantly much higher in those primed with MenC-TT (Pace et al., 2015). Such differences could be due to the type of carrier protein used (a carrier protein is the protein to which the polysaccharide is attached to), specifically tetanus toxoid being a stronger immunogen than CRM197 (Richmond et al., 2001) when used for priming as well as when the same TT carrier protein is used for priming and boosting. The greater number of memory B-cells measured in subjects primed with MenC-TT and boosted with Hib-MenC-TT compared with those primed with MenC-CRM197 further strengthens this argument (Khatami et al., 2014). However, differences in the conjugation chemistry, the type of MenC oligo/polysaccharide used in the vaccine as well as other differences in vaccine formulations between different manufacturers could explain immunogenicity differences seen between the different MenC glycoconjugates. Such observations can determine the MenC vaccine formulation used for priming and boosting infants when a MenC vaccination schedule is planned.

This study was the first to demonstrate the use of a MenC glycoconjugate vaccine as a probe for immune memory (Pace et al., 2016), when classically previous studies used a pure polysaccharide MenC vaccine formulation to challenge primed subjects, a practice that raises concerns on the induction of hyporesponsiveness. MenC priming in infancy is important to generate high post boost MenC rSBA GMTs as shown by the higher proportion of subjects with MenC rSBA GMTs ≥1:8 and higher MenC rSBA GMTs in those primed in infancy compared to those who received their first MenC conjugate vaccine dose at 12 months of age (Pace et al., 2016). The magnitude of MenC rSBA GMTs, GMRs and adjusted GMFRs at 6 days post boost may be used to distinguish primed from unprimed children. Again differences in the immune kinetics were seen between the different MenC conjugate vaccine prime and boost schedules used with significantly higher MenC GMTs (figure 4), GMRs and adjusted GMFRs seen at 6 days after the Hib-MenC-TT boost in those primed with MenC-TT compared to priming with a single or two dose MenC-CRM197 vaccine schedule in infancy. Antibody decline from the 6th to the

28th day post the Hib-MenC-TT boost was also slower in those primed with MenC-TT compared to MenC-CRM priming (figure 4) (Pace et al., 2016).

5 Practical significance of the study data

How can the findings of this trial be implemented on a practical level? In an epidemiological study by Pace et al. (2020) looking at meningococcal disease in Malta over an 18 year period, from 2000- 2017, it was demonstrated that infants had the highest age specific incidence rates of IMD at 18.9/100,000 population with the incidence of capsular group B, C and W disease being significantly higher than in all other age groups. Furthermore, although there was a declining trend in MenB disease in the population, reflecting natural variation in MenB disease, the overall incidence of IMD remained stable. This was a result of the stable incidence of MenC disease as well as the appearance of MenW and Y disease in the population (Pace et al., 2020). The overall stability of the incidence of MenC disease (0.25/100,000 population from 2000-2008 compared to 0.33/100,000 population from 2009 – 2017) was in sharp contrast to the declining incidence of MenC disease in Europe dropping significantly from 0.22 to 0.1 over the same time periods as a result of the MenC vaccination programmes introduced within several European countries as discussed by Pace et al. (2020). This demonstrated the urgent need to introduce a MenC, as well as a MenB vaccination programme, in Malta. The single prime and boost MenC vaccine schedule introduced in Malta in 2020 is again supported by the findings from the study above, although the findings were extrapolated to the use of a MenACWY conjugate vaccine, which was more pragmatic considering the appearance of MenW disease in infants and MenY disease in adolescents (Pace et al., 2020). Although the impact of this schedule on MenC disease is still to be seen, a one-time catch up campaign would have been crucial to induce herd protection against MenC disease, as observed in other countries.

6 Conclusions

Vaccines are an extremely important tool in the prevention of infectious diseases. The way vaccines are scheduled on immunisation programmes is a dynamic process that reflects the availability of immunogenicity and safety data from vaccine trials as well as the epidemiology of the infectious diseases the vaccines are aiming to prevent, especially for those infections which are prevalent in children. This underlines the importance of conducting clinical vaccine trials in children. Having a vaccine research centre in Malta would facilitate collaboration in vaccine trials being conducted in Europe and would push Malta to the forefront of clinical vaccine research.

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