The Capstone Committee for Charles Brent Chesson

Certifies that this is the approved version of the following capstone:

Comparison of current evidence from randomized clinical trials and observational studies for immunogenicity in variable meningococcal C vaccine schedules in children, adolescents, and adults

Committee:

Christine M. Arcari, PhD MPH
Chair

Alan D.T. Barrett, PhD

Sreenivas P. Veeranki, MBBS DrPH

_____

Dean, Graduate School

Comparison of current evidence from randomized clinical trials and observational studies of immunogenicity in variable meningococcal C vaccine schedules in children, adolescents, and adults.

by

Charles Brent Chesson, BS

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Comparison of current evidence from randomized clinical trials and observational studies for immunogenicity in variable meningococcal C vaccine schedules in children, adolescents, and adults.

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Charles Brent Chesson, MPH

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Supervisor: Christine Arcari

Abstract: *Neisseria m.* serogroup C protein conjugated vaccines are licensed globally for the prevention of meningococcal disease. Vaccine schedules are determined according to region specific epidemiology are optimized to provide immune protection using the fewest number of doses necessary. Lowering or optimizing vaccine schedules can dramatically impact health care associated costs and patient compliance. We systematically reviewed the available evidence from clinical trials and follow-ups of meningococcal C quadrivalent, bivalent and monovalent vaccines in all age ranges. We searched PUBMED/Medline, EMBASE, Cochrane Central Register Controlled Trials (CENTRAL) and the Global Index Medicus databases during 2000-present, including internal referenced studies where relevant. Quadrivalent, bivalent, Hib-containing and monovalent conjugate vaccines were immunogenic in all age groups starting at 2 months of age. Even as early as age 10, older age correlated with increased duration of protection. Seroprotective antibody titers in infants were short-lived after primary schedule vaccinations were completed, and by 12 months of age, only 40-69% of subjects retained defined titers adequate for short term protective immunity. Combined vaccinations with routine childhood immunizations were well tolerated. Available evidence suggests that 2 or fewer doses during infancy is highly effective and immunogenic, even beginning as early as 2 months of age. In nearly all schedules, tetanus toxid (TT) carrier vaccines were more immunogenic than their diphtheria toxin mutant 197 (CRM or CRM197) protein carrier equivalents. This was less pronounced with 3 doses in infancy, and by 12 months of age antibody titers waned similarly regardless of the vaccine used. Single or booster doses given at 1-10 years of age maintain protective serum titers for 3 years in approximately 60% of children. A single or booster dose given after 11 years of age is expected to provide immunity for approximately 75% of children over 5-7 years.

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List of Abbreviations

CRM197	Diphtheria toxin mutant at position 197
DT	Diphtheria toxoid
GMT	Geometric mean titer
Hib	Haemophilus influenza type b
PCV	Pneumococcal vaccine
SBA	Serum bactericidal antibody; Serum bactericidal assay
rSBA; hSBA	Serum bactericidal antibody as measured by rabbit or human complement
RCT	Randomized controlled trial; randomized clinical trial
TT	Tetanus toxoid
WHO	World Health Organization

Chapter 1

Introduction

Vaccine schedules should be tailored to satisfy the distribution and prevalence of disease within a given nation. The implemented schedule is particularly important in resource limited settings usually found in low- and middle-income countries. These countries must often choose between the most impactful vaccines to implement while forgoing other needed vaccines, and decisions on the optimal dosing strategy are often made on the basis of cost, instead of optimal immune protection [1]. Policy makers that decide the countries vaccine schedules and dosing regimens look into the scientific evidence for clear recommendations on an appropriate schedule; however the amount of literature on different dosing regimens is overwhelming and highly technical. Our report consolidates the current literature from clinical trials and full up studies to aid stakeholders in making informed policy decisions and directing future research needs to address gaps in knowledge. A systematic review on meningococcal group C vaccine schedules was conducted in 2005 [2], however it did not include many of the new protein conjugate serogroup C vaccines, nor the bivalent and quadrivalent formulations that many countries favour due to their consistent and durable immune protection in comparison to polysaccharide meningococcal vaccines[3].

The objective of this systematic review is to examine all data published from 2004 to 2015omparing schedules of meningococcal C vaccines for infants, children, and adults for enhanced vaccine efficacy and long term immunity as demonstrated through evidence of serogroup C serum bactericidal antibodies.

The primary question and purpose of this review is to ascertain which vaccine schedules for protein conjugate meningococcal vaccines result in superior immunological protection, based on the current laboratory standards of serum bactericidal antibody (SBA) titres (test with human serum complement of <1:4, or <1:8 using rabbit serum complement component) in infants (2-11 months), children and adolescents (1-18 years) and adults (18 years and above).

We will address the following secondary questions:

1. Does primary vaccination with the Meningitis C quadrivalent or bivalent conjugate vaccine co-administered with Hib vaccine provide superior protection compared to monovalent Meningitis C vaccines?
2. Does co-administration of MMR, DTP, or other single or combined vaccine with Meningitis C conjugate vaccine alter efficacy or safety?
3. How long can patients expect to maintain circulating protective antibody titers by age group and type of vaccine administered?

Our research aim is to provide a comprehensive and exhaustive review of up-to-date meningococcal serogroup C vaccine formulations that are either approved or in clinical phase development to aid policy makers in choosing the appropriate vaccine and optimizing dosing schedules. Further, this review will seek to uncover the current gaps in knowledge to direct future research in the field.

Chapter 2

Background

Neisseria meningitidis is the major etiological agent of bacterial meningitis worldwide and represents a significant global health burden, particularly in developing countries. Invasive meningococcal disease can result in severe life threatening complications including meningitis and septicaemia. Globally, cases from N. *meningitidis* infection are estimated at around 1.2 million per year resulting in 135,000 deaths [4]. This particular high fatality rate ranging from 5 to 15% can occur even with the presence sufficient medical services. Long term sequelae can include significant brain damage and permanent hearing loss, attributing to increased hospital costs and burden. Incidence rates can reach as high as 1000 cases per 100,000 along the meningitis belt in Africa, although in developed countries disease rates typically remain between 0.1-10 cases per 100,000 [5]. Distribution of disease across age groups can also vary widely. In the United States (U.S.) alone, over 70% of all cases of bacterial meningitis occur in young adults ~18 years of age living in close quarters where as in low and middle income countries meningitis typically occurs in infants and toddlers.

Small outbreaks in endemic regions are common although in many countries disease can be highly episodic leading to large outbreaks. This is most notably seen along the African meningitis belt which stretches from Senegal to Ethiopia in sub-Saharan Africa, cycling between large outbreaks every 3-7 years and smaller annual outbreaks during the dry season during December-June every year [6]. Major risk factors contributing to bacterial meningitis include overcrowding, smoking, and immunosuppressive disorders such as AIDS and genetic disorders. The annual Hajj pilgrimage is a common location for large outbreaks of meningococcal disease seen from overcrowding due to high levels of transmission [7].

N. *meningitidis* is a diplococcal, gram negative bacterium that regularly colonizes the nasopharynx in humans yet remains asymptomatic in a majority of carriers. This pathogen is transmitted primarily through infectious aerosolized droplets and secretions of the respiratory mucosa. Close or direct contact with asymptomatic or preclinical carriers can lead to transient passage, colonization, or serious disease. Thirteen serogroups exist and are distinguished by their unique capsular polysaccharide.

Of the 13 serogroups, six (A, B, C, Y, W, and X) account the overwhelming majority all serious infections, and serogroup C is endemic to the Americas, Europe, Asia and parts of Africa and Australia [8]. The highest endemic rates of disease from serogroup C were reported in Europe and the United Kingdom (UK), but the incident rates have been dramatically reduced due to the development of serogroup C monovalent and quadrivalent conjugate vaccines and their inclusion in routine scheduled vaccine programs [9, 10].

Meningicoccal C vaccines are available as polysaccharide bivalent (A and C), trivalent (A, C, W), or quadrivalent (A, C, W, Y) and as polysaccharide-protein conjugates. These conjugate vaccines are available as monovalent, bivalent (C and Y) co-administered with Hib vaccine, or quadrivalent formulations. Conjugate vaccines are preferred due to their approved use in young children and their ability to induce enhanced immunological memory, persistent circulating antibodies, and herd immunity through decreased carriage and transmission compared to polysaccharide alone equivalents [11, 12].

Studies from the 1960's provide evidence that serum bactericidal antibody (SBA) titers ≥4 correlated strongly with protection from meningococcal serogroup C disease. This assay requires an exogenous source of complement and today complement preserved baby rabbit sera is the most common and commercially available source. Rabbit complement requires higher SBA titers than those measured with human complement, and it is accepted that for serogroup C, rabbit SBA titers of ≥8 are equivalent as correlates of protection and a proxy for vaccine effectiveness [13].

Current World Health Organization (WHO) recommendations for areas with high to moderate endemic incidence rates of meningococcal disease advocate the introduction of large scale vaccination programmes while those countries with low incidence rates should introduce programmes which target vaccination for targeted high risk groups. WHO guidelines for monovalent serogroup C conjugate vaccine schedules for high risk children aged 2-11 months are administered as a 3 dose series, with 2 months gap between first and second dose, and one year gap between second and the third; or as a single dose for children aged 1 year or older. Quadrivalent meningococcal conjugate vaccines are currently licensed as a 2 dose series beginning at 9 months of age with a 3 month gap between the second dose, or as a single dose injection for those 2-55 years of age. Polysaccharide vaccines are endorsed in cases

where economic resources are limited or protein conjugate vaccine supplies are scarce. All polysaccharide meningococcal vaccines are administered as a single dose for those aged 2 years and older.

Chapter 3

Methods

We will identify and critically appraise the best available evidence that addresses clinically important outcomes and provide an evidence profile that summarises the findings for each outcome. This review will follow the guidelines for undertaking systematic reviews as described in the Cochrane Handbook [14]. Articles for inclusion were based on randomized clinical trials and observational studies for efficacy in variable meningitis C vaccine schedules in children, adolescents, and adults.

A. Vaccines Included:

Meningitis C vaccines of the following types are will be considered:

1. Monovalent conjugate: (TT conjugated, NeisVac-C® (Baxter/GSK); CRM197 conjugated Menjugate® (Novartis), Menactra® (Aventis Pasteur), Meningitec® (Nuron Biotech).
2. Bivalent conjugate: Serogroups A+C; Serogroups C+Y; MenHibrix® (GSK), and HiB + NmC Menitorix® (GSK)
3. Quadrivalent: (DT conjugated, Menactra® (Sanofi-Pasteur); CRM197 conjugated, Menveo® (Novartis), or TT conjugated, Nimenrix® (GSK).
4. Any formulations similar to the above licensed vaccines.

B. Exclusion Criteria

Studies will be excluded if any of the following criteria are met:

1. Study is not conducted in humans with appropriate controls and selection criteria that minimize any bias in the results or data presentation.
2. The study's authors have financial interests in results of the study.
3. Study evaluates any vaccine in which development has been discontinued.
4. Study is unpublished or data is from an interim report.

C. Search Strategy

The following electronic databases will be searched from January 2004 to June 2014 without language restrictions for published or accepted studies:

1. PubMed MEDLINE
2. EMBASE OvidSP
3. Cochrane Central Register of Controlled Trials (CENTRAL)

- Global Index Medicus (WHO) consisting of the following databases: African Index Medicus (AIM), Index Medicus for Eastern Mediterranean Region (IMEMR),Latin American & Caribbean Health Sciences Literature (LILACS), Index Medicus for South-east Asia Region (IMSEAR), and Western Pacific Region Index Medicus (WPRIM).

A detailed search string is included in the Appendix A of this review. Additionally, we searched relevant references in studies identified through our outlined search methodology and previous systematic reviews for articles that met our inclusion criteria. Search terms will use Medical Subject Headings (MeSH) from 2004 – present for terms specific to each database and will include terms relating to:

- Meningitis, Meningococcal
- Neisseria meningitidis serogroup C
- Meningococcal vaccines
- Conjugate vaccine
- Randomized controlled trials

D. Outcomes

Our primary outcome of interest is vaccine efficacy. Due to the low incidence of meningococcal disease, we did not identify any clinical trials on clinical efficacy. Our primary measure and means of comparison were surrogates of protection defined as ≥1:8 and ≥1:4 SBA using rabbit or human serum complement component respectively [15, 16]. To be eligible for inclusion each study must include immunogenicity data reported by SBA determination of antibody titres with either human or rabbit complement.

E. Data Extraction

We extracted the data including but not limited to the study design, vaccine(s) used, schedule, laboratory assay, co-administered vaccines, age group(s), reported numerical data into excel. Data extraction forms were designed by the authors specifically for this review. In some cases where graphical data were presented, we extracted the numeric data using PlotDigitizer.

F. Grading of trials [17]

Trial grading was determined from the following questions:

1. Was the study described as randomized?
2. Was the study conducted "double-blind?"
3. Was a description of withdrawals and dropouts included?

One point was given for use of the word random, randomization, or randomly in the study methods in such a way that it is not possible to predict treatment assignment and each participant had an equal chance of receiving the given intervention(s). An additional point was assigned if the method of randomization was described and appropriate.

If the word "double-blind" was used in describing the study methods, we assigned one point. Double-blinding approach refers to wherein both the study participant and the person conducting the assessment are not able to identify the intervention. An additional point was assigned if the method of blinding was described in the text, such as placebos or identical treatments.

Withdrawals and dropouts are participants who did not complete the study in its entirety. The number and reasons for withdrawal must be shown or available. No point was assigned if a statement or figure about withdrawals or dropouts was not presented.

G. Assessment of bias [17]

For each study included we assessed the risk of bias in the study according to methods of randomization, allocation concealment, blinding of participants and personnel, incomplete outcome data, and assessment of selective reporting. Bias was graded as low, unclear, or high. 'Low' risk of bias was interpreted as unlikely to seriously influence the outcomes and 'unclear' as may put the outcomes into question. If two or more of these items were not explicit, we labelled the study unclear. If the study had either randomization, allocation concealment or method of blinding stated the study was labelled as low risk of bias.

Chapter 4

Results

A. Overview of studies

The electronic searches identified 745 abstracts after excluding for duplicates. We reviewed these abstracts and identified 159 studies as potentially eligible. After a full text review, 63 studies were found to have met the inclusion criteria and were included. Of the 63 included studies, 10 studies were observational in nature, and generally were followed-up for an existing randomized controlled trial or cohort of a large mass vaccination campaign. The remaining 52 studies were controlled trials, two of which did not include randomization.

In cases where multivalent formulations were used the extracted data were only reflective of immune responses to serogroup C conjugate vaccine. We did not make comparisons to polysaccharide only vaccines as they have demonstrated to be inferior in numerous studies to protein conjugated counterparts [16, 18-20]. Data on adverse events were not included although serious adverse events were rare and not attributed to vaccination. Several comparison studies are included of co-administered routine childhood vaccines with meningococcal vaccine as either single dose formulations or simultaneous administration. We did note in the text that routine vaccinations such as whole cell pertussis (wP) administered as some childhood vaccines have been shown to boost the immune response to MenC polysaccharide. Co-administration studies with infant series vaccines including Rotavirus, Hepatitis B (HBV), Haemophilus influenza B (Hib), Diptheria-Tetanus-acellular Pertussis (DTaP), inactivated Polio (IPV), Pneumococcal conjugate vaccine (PCV), and MMR were demonstrated to be safe [21-23]. Immune responses to meningococcal C vaccines when co-administered with other immunizations were not considerably affected.

Our search yielded many studies on single dose basic immunogenicity and safety of investigational monovalent and quadrivalent vaccines at day 28 post vaccination. These randomized controlled trials were excluded unless long term antibody persistence was included in the data or the study was performed in infants, toddlers or young children. All included studies are listed by type of

vaccine in tables 1, 2 and 3 below. These tables include our grade and assessment of bias, as well as age group(s), immunization strategy, carrier protein and year of publication.

I. Quadrivalent Vaccines

1.1 – (3+1) 4 dose schedule
Snape 2008[24]; Klein 2011[25] Tregnaghi 2014[26] – CRM197 protein carrier

Snape evaluated the immunogenicity of several different dose schedules including 2, 3, 4 or 2, 4, 6 months each with a 12 month booster. Concomitant co-administration of DTaP-Hib-IPV-HBV and PCV7 were given according to the country-specific schedule. At 12 months, the 2, 3, 4 month schedule resulted in 60% (95% confidence interval (CI): 47-72%) of individuals maintaining protective titres compared to 70% (95% CI: 54-82%) in the 2, 4, 6 months. However, the latter group did not respond to the 12 month booster as geometric mean titers (GMT) pre-boost was 13 (95% CI: 8.72-18 [hSBA] compared to only 11 (95% CI 6.59-17.0 [hSBA] one month post boost [Figure 1A]. Post boost the 2, 3, 4 month cohort GMT rose from 7.94 (95% CI: 11-5.84 [hSBA]) to 429 (95% CI: 288-639 [hSBA]) <<cite Snape paper>>. Contrastingly, Klein also reported on a 2,4,6 month primary series with a 12 month booster in which the cohorts from both studies had similar antibody titers at 7 months, yet this cohort responded to the booster dose increasing GMT from 11 to 227 (95% CI unavailable) 1 month after the booster. Study by Tregnaghi and colleagues included schedule at 2, 4 and 6 months and found that 97% of infants with >1:8 hSBA (GMT=150 [hSBA]) at 7 months, which dropped to 26% (GMT=4.1 [hSBA]) pre boost at 16 months of age.

1.2 (2+1) 3 dose schedule
Blanchard-Rohner 2013[27]; Perrett 2008[28]; Snape 2008[24]; Tregnaghi 2014[26] – CRM197 protein carrier

Three studies investigated a 2- and 4- month of age primary schedule with a 12 month of age booster dose (DTaP-Hib-IPV co-administered, with MMR at boost). The vaccine formulations used in these three studies were almost identical except for the addition of aluminium phosphate as an adjuvant in the study conducted by Snape *et al*. After primary series vaccinations, 96-84% of patients had geometric mean titers greater than 1:4 hSBA. Perrett (DTaP-Hib-IPV-HBV co-administered,

MMR+PCV at boost) only reported to the five month time point but Rohner and Snape were in general agreement at 12 months where percent seropositive (by >1:4 hSBA) dropped to 40-48% [Figure1B], with the largest decrease in GMT over 5.5-8 months of age. At 13 months, 1 month after the booster dose, nearly all patients, 100-96% had seroprotective titers over the three studies. In a study by Tregnaghi and colleagues whose immunization schedule included administering doses at 2 and 6 months followed by a booster at 12 months, a slightly higher percentage of infants remained protected (>1:8 hSBA) at 12 months compared to the studies by Rohner *et al*. and Snape *et al*.

1.3 (1+1) or (2+0) 2 dose schedule
Halperin 2009[29] and 2010[30]; Klein 2012[31]; Snape 2008[24]; Tregnaghi 2014[26] – CRM197 protein carrier.

Five alternative schedules using a two dose regimen are presented in four studies across several age groups. Concomitant vaccines administered were DTaP-Hib-IPV and PCV7. The earliest schedule used was 2 and 4 months of age. As discussed above but without the booster, Snape reported strong immunogenicity after the second dose at 5 months of age with 84% (95% CI: 92-74%) and 91% (95% CI: 96-81%) in UK and Canadian cohorts respectively reaching protective serum antibody levels. These titers waned considerably and at 12 months only 40-48% retained seroprotective antibody titers. Halperin reports two different two dose regimens, 6 and 12 months, and 12 and 18 months. However, the latter schedule primes with a monovalent serogroup C vaccine (Menjugate® Novartis Vaccines). After the first dose at 6 months of age, 93% (95% CI: 98-84%) were protected, which decreased to 86% (95% CI: 94-74%) by 12 months of age. All patients responded to the booster dose with a GMT of 314 (95% CI: 421-234 [hSBA]). The alternate regimen of 12 and 18 months produced similar immune responses although GMTs were marginally higher, resulting in more toddlers above the threshold 94% (95% CI: 99-82%) and 91% (95% CI: 97-78%) of them remaining there until the 18 month dose [Figure 1C]. As before, all patients responded robustly to the booster dose. A similar schedule of 12 and 15 months was reported by Tregnaghi resulting in 91% and then 100% >1:8 hSBA after each dose with a nearly a log increase in hSBA GMT after the second dose, 45 to 501. Study by Klein *et al*, with doses administered at 8 and 12 months demonstrated similar results. Hundred percent of patients had >1:8

(hSBA) serum dilutions at 13 months, or 1 month following the second dose. In a slightly older age group of 2-5 years, Halperin *et al*. presented a two dose regimen separated by 60 days, and found that 98% (95% CI: 99-95%) of children were seroprotected at 1 month following the last dose.

1.4 Single dose schedules

A. Diphtheria conjugated

Bashir 2005[32]; Vu 2006[33]; Keyserling 2005[34]; Pichichero 2005[35] Baxter 2009, Gill 2010, Jackson 2009[36-38]; Patel 2014[39]

The vaccines used in each of the four studies with ACWY-DT quadrivalent vaccines were identical formulations. Two studies investigated single dosing in young children <<cite the two studies>>. In 2-5 year olds, Bashir reported 100% of children protected after 1 month (GMT=12535 (95% CI: 18688-8408 [rSBA]), although these children had previously received a single dose of monovalent serogroup C conjugate vaccine (minimum one year since vaccination; previous schedule and number of doses unknown). In a similar study by Pichichero, serogroup C naïve 2-10 year olds were immunized (mean age 3.7 years) with one dose and 87.9% (95% CI: 91.2-83.9%) were above the threshold of protection (GMT=354 (95% CI: 407-308 [rSBA]) after one month. Three studies were identified where adolescents and young adults aged 11-18 were immunized with a single dose of vaccine. Keyserling reported 98.9% (no CI available; GMT 1924, 95% CI: 2228-1662 [rSBA]) were seroprotected after one month, which decreased to a GMT of 211 (95% CI: 370-121 [rSBA]) after 3 years. Using the same cohort, Vu *et al*. reported GMTs of approximately 8.3 (95% CI unavailable [hSBA]) at the 3 year time point. This degree of variability is in part due to the different complement components used for the assays. Baxter compared carrier proteins up to three years in 11-18 year olds with ACWY-DT and ACWY-CRM vaccines and found that at all time points the percentage with MenC rSBA >1:8 was similar in the two groups with 62-64% above the 1:8 threshold of protection after 3 years. In a final single dose study in adults 17-37 years of age, Patel assessed the persistence of antibody responses up to three years and reported that after six months, 87% of adults had rSBA >1:8 which decreased to 54% after 3 years.

B. CRM197 conjugated

Halperin 2010[28] & 2010[30]; Klein 2011[25]; Jackson 2008[40] Black 2009[41]

Halperin reported that a single dose of CRM conjugated quadrivalent vaccine administration at 12 months of age resulted in 94% (95% CI: 100-87%) protection 1 month post vaccination with reported GMTs were 40 (95% CI: 53-29 [hSBA]). Klein *et al* reported similar results in the same age group; GMTs = 35 (no CI available [hSBA]). Halperin also reported 60% and 63% seropositivity in 2-5 years and 6-10 years aged children with single dose of vaccine administration. In the same study these age groups were given an equivalent dose of DT conjugated ACWY that was shown to be statistically non-inferior however the GMTs were lower in the DT conjugated group [Figure 1D]. Across a wider age range, 2-10 year olds, Black reported at one month and 12 months post immunization 83% (95% CI: 87-78% [hSBA], and 68% (95% CI: 74-62 [hSBA] reported >1:4 hSBA titer. Older age groups, 11-17 years of age, were more responsive to a single dose, with 84% (95% CI: 90-77%) >1:8 (hSBA) serum dilution that slightly decreased to 77% (95% CI: 84-69%) after 12 months (adjuvant-free formulation).

C. Tetanus toxoid conjugated
Knuf 2012[42]; Vesikari 2012[43, 44]; Østergaard 2008[45] & 2013[46]; Dbaibo 2013[47]

All the included studies using TT as the carrier protein were single dose studies conducted in children with ages 12 months and older. We compared studies only from identical vaccine formulations. Knuf reported 12-14 month old toddlers sampled at 1 month post prime were 100% (95% CI: 100-90.7%) seroprotected and decreased to 92.3% (95% CI: 98.4-79.1%) after 15 months. From the same study, 3-5 year olds sampled 1 month post prime were 100% (95% CI 100-92.3%) seroprotected and seroprotection remained same at a 15 month follow-up time point. Results from Vesikari demonstrated that children 1 to 2 years of age were 100% (95% CI 100-98.3%) seroprotected after one month, decreasing to 90.8% (95% CI 94.7-85.5%) after 3 years. This is in agreement with another study by Vesikari with single dose priming in 2-10 year olds in which 100% (95% CI: 100-98.4%) had positive rSBA at ≥1:8 titre after one month, and after 3 years, 98.4% (95% CI: 99.7-95.5%) of individuals maintained seroprotective titers. In agreement with this are two studies from Østergaard who immunized 15-25 year olds and reported GMTs (258.4 and 532.7) at 30 and 36 months post vaccination respectively [Figure 1e]. This corresponds to 100% of young adults remaining above the threshold of protection for antibody titers 3 years post vaccination. However, in adults over the age of 56, vaccine

responses were variable, 80.3% (85.7-73.9% 95%CI) were defined as vaccine responders, and decreased slightly with age.

Figure 1.

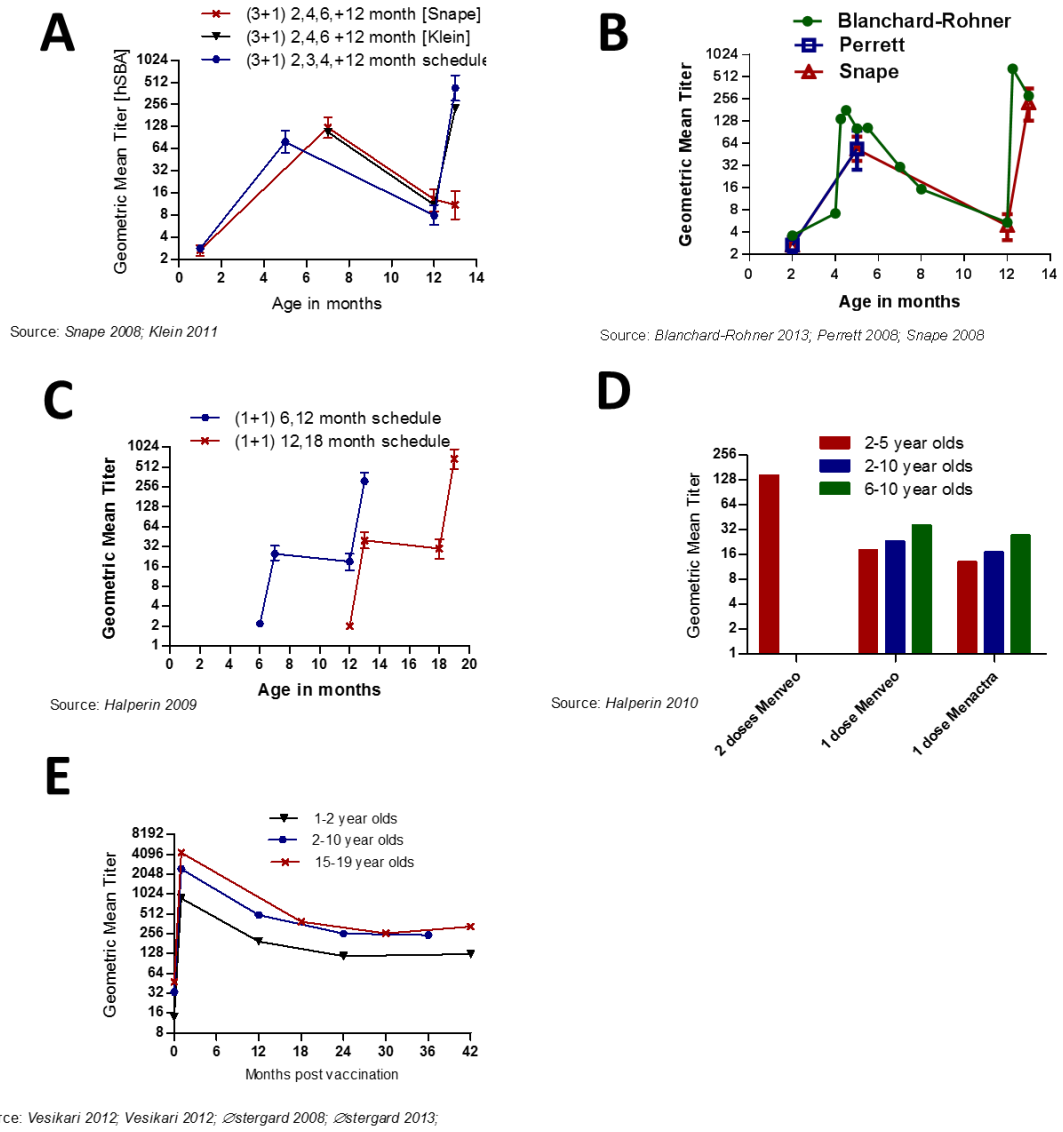

Figure Caption 1. Quadrivalent ACWY vaccines Comparison of 3, 2 or 1 dose primary series vaccinations with quadrivalent vaccines covering serogroups ACWY and long term antibody persistence. (A) 3 dose primary with 12 month booster, CRM197 carrier protein *[Snape 2008; Klein 2011]* (B) 2 dose primary schedule with 12 month booster. Mean values plotted over 3 studies, CRM197 carrier protein *[Rohner 2013; Perrett 2008; Snape 2008* (C) 2 doses separated by 6 months in infants and toddlers, CRM197 carrier protein *[Halperin 2009]* (D) Comparison of one or two doses of CRM197 carrier quadrivalent vaccines or single doses between CRM197 or DT carrier vaccines across multiple age groups in children and young adults *[Halperin 2010]*. (E) Long term GMT persistence up to 42 months post vaccination after a single dose of TT-conjugated quadrivalent vaccine across several age ranges of vaccine administration [*Vesikari 2012 & 2012; Østergard 2008 & 2013*].

Author	Design	Carrier Protein	Age Group	Year Published	GRADE	Risk of Bias
Bashir	RCT	DT	2-5 year olds	2006	4	Low
Pichichero	RCT	DT	2-10 year olds	2005	5	Low
Keyserling	RCT	DT	11-18 yrs	2005	5	Low
Baxter	RCT	DT&CRM	11-18 yrs	2014	3	Low
Patel	Cohort	DT	17-37 years	2014	1	Unclear
Vu	RCT Follow-up	DT	11-18 yrs	2005	2	Unclear
Klein	RCT	CRM197	toddlers	2011	2	Unclear
Halperin	RCT	CRM197	6-12 month olds	2009	3	Low
Black	RCT	CRM197	2-10 year olds	2009	3	Low
Jackson	RCT	CRM197	11-17 year olds	2008	2	Low
Halperin	RCT	CRM197	2-5 & 6-10 year olds	2010	3	Low
Rohner	RCT	CRM197	infants	2013	2	Unclear
Perrett	RCT	CRM197	infants	2008	3	Low
Klein	RCT	CRM197	infants	2012	3	Low
Snape	RCT	CRM197	infants	2008	3	Low
Tregnaghi	RCT	CRM197	infants	2014	3	Low
Dbaibo	RCT	TT	adults >55 yo	2013	3	Low
Vesikari	RCT	TT	12-23 months	2012	3	Low
Vesikari	RCT	TT	2-10 yrs	2012	3	Low
Østergaard	RCT	TT	15-19 yrs	2013	3	Low
Knuf	RCT	TT	12-14 mos ; 3-5 yrs	2012	3	Low
Østergaard	RCT	TT	15-25 years	2008	3	Low

Table 1A. Descriptive data table of quadrivalent vaccines included in this review. Included studies are grouped by the type of carrier protein.

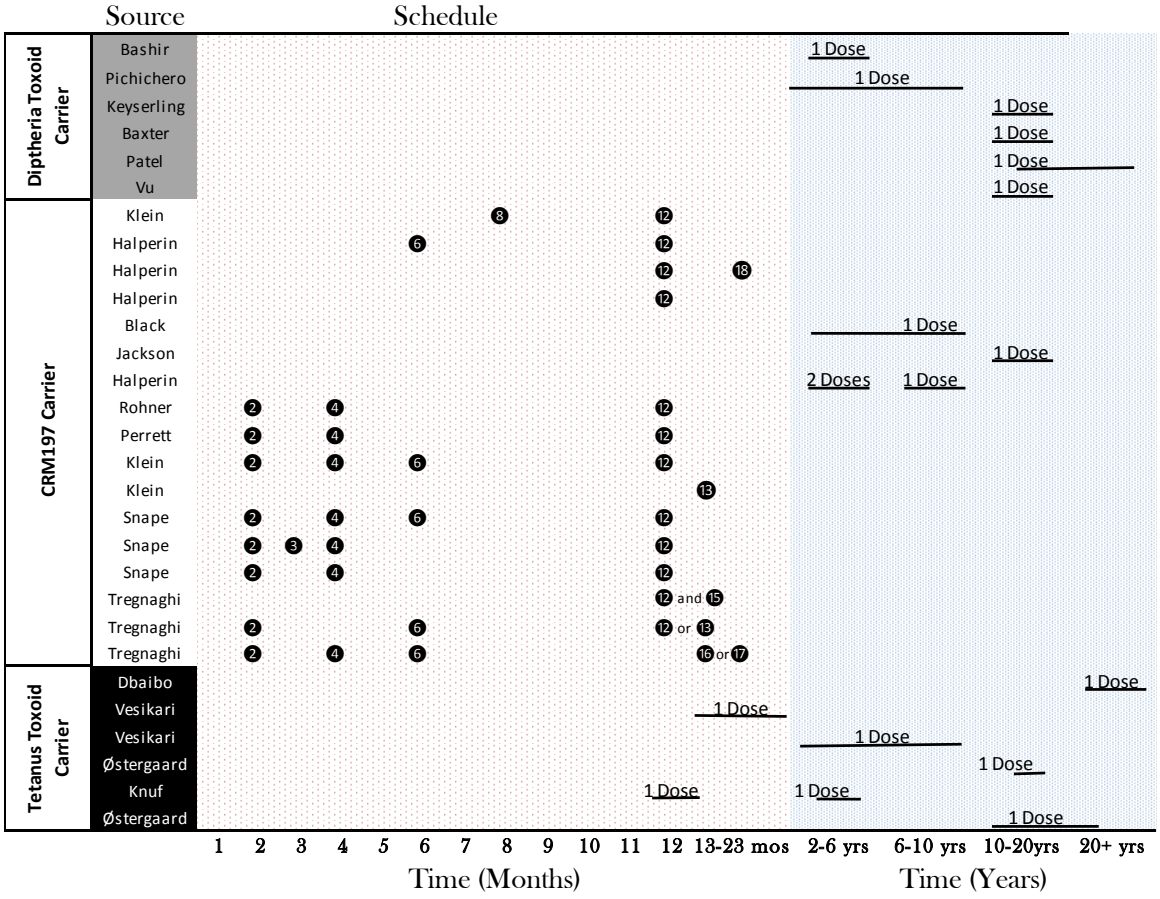

Table 1B. Visual data table of quadrivalent vaccine dosing schedules, grouped by the type of carrier protein, from the studies included in this review.

II. Bivalent (A+C; C+Y) and Hib combination vaccines

A. Hib containing serogroup C conjugated vaccines

2.1 (3+1) & (3+0) doses using a 2, 3, and 4 month primary schedule-

Pace 2007[48] & 2008[49]; Schmitt 2007[50]; Khatami 2011[51] & 2012[52]

In a two study series from Pace *et al*, infants were immunized at 2, 3 and 4 months in a primary series (Hib-MenC-TT+DTaP-IPV) with a booster (Hib-MenC-TT+MMR) at 12 months of age. GMTs were reported as 581.1(95% CI: 656.2-514.7 [rSBA]) at 5 months of age with 99.2% (95% CI: 99.8-97.5%) having ≥1:8 rSBA positive titers. GMTs decreased in the next 7 months such that 78% (95% CI: 82.3-73.3%) of children were reported to have ≥1:8 rSBA positive titers. One month post boost at 12 months age GMTs rose to 2193.7 (95% CI: 2558.1-1881.1 [rSBA]), which was substantial compared to the booster group (MenC-CRM197) GMT 477.9 (95% CI: 639.2-357.3 [rSBA]) [Figure 2A].

Schmitt *et al.* published a report employing the same primary schedule (co-administered+ DTaP-HBV-IPV) at 5 months of age and reported GMTs at 944.2 (95% CI: 1143.8-779.4 [rSBA, 5ug group C PS]) that waned to 159.3 (95% CI: 235.3-107.9 [rSBA]) at 12 months similar to other treatment groups. GMT's one month post challenge were substantially higher in the Hib-MenC-TT group at both 5 and 10μg concentrations, although the 5μg gram dose resulted in the highest titer post challenge from any group [Figure 2B]. In a long term antibody persistence study with Hib-MenC-TT (+DTaP-IPV), Khatami *et al*. reported after a 2, 3, and 4 month primary dose schedule followed by a booster dose at 12-15 months of age, seroprotection (>1:8 rSBA GMT) decreased from 89% (95% CI: 93-83.8%; GMT=123 95%CI: 153-98) at one year post booster down to 59.3% (95% CI: 66.3-52%; GMT=30.4 95%CI: 40.4-22.9) at five years after the booster dose in contrast to the MenC-CRM197 group where 44.8% (95% CI: 58.5-31.7%; GMT=11.3 95%CI: 16.5-7.7) retained titers >1:8 [rSBA] after 5 years [Figure 2C].

2.2 (3+1) and (3+0) doses using a 2, 4, and 6 month primary schedule

Tejedor 2007[53] & 2012[54]

Tejedor *et al*. investigated a 2, 4, and 6 month primary schedule (co-administered with DTaP-HBV-IPV), following-up with a long term persistence sampling after a booster at 12 months of age. One month following the primary series final dose, reported GMTs were 2467.1 (2975.3-2045.7 95%CI) with 100% of individuals greater than or equal to the 1:8 positive titer threshold [rSBA]. The same cohort was given a 12 month booster dose and sampled every 12-18 months for 5.5 years. Antibody titers waned most notably 18 months post boost, but stabilized from 2.5 to 5.5 years after the booster to 121.5 (95% CI: 207.9-71.0 [rSBA]) corresponding to 82.6% (95% CI: 92.2-68.6%) of those maintaining seroprotective antibody titers. This same study compared a heterologous prime boost treatment arm, primed with MenC-TT (2 dose primary schedule at 2 and 4 months +DTaP-HBV-Hib-Polio) and boosted with the combination vaccine Hib-MenC-TT. GMT's were consistently higher throughout the long term follow-up, although they received fewer overall doses of serogroup C vaccine. 5.5 years post boost, 94.1% (95% CI: 97.8-87.5% [rSBA]) of children maintained greater than 1:8 rSBA compared to a control MenC-CRM197 cohort (3 dose primary schedule at 2, 4, and 6 months +DTaP-HBV-Hib-Polio) at 60.9% (74.9-45.4% 95% CI [rSBA]) [Figure 2D].

2.3 (2+1) doses

Vesikari 2012[55]

Vesikari vaccinated infants on a 3 and 5 month primary schedule (co-administered with DTaP-HBV-IPV) followed by a booster dose at 11 months of age. Primary series response at 6 months of age yielded GMTs at 466.1 (95% CI: 543.7-399.5) which waned considerably by 11 months of age, yet responses to the booster dose increased to 1861.8 (95% CI: 2105.6-1646.2 [rSBA]) one month post boost. This corresponds to 99.1% (95% CI: 99.8-97.3%) and 100% (95% CI: 100-98.8%) seroprotected at the corresponding time points [Figure 2E]. Comparatively the antibody titers from positive SBA were higher in the comparison MenC-TT group at all time points from this study.

2.4 Multidose study with long term follow-up

Perrett 2010[56]

Perrett followed-up with children immunized during the introduction of the Meningitis C vaccine in the UK 6 years after receiving 1, 2, or 3 doses of monovalent Meningitis C vaccine in infancy to childhood (routine childhood immunizations that were co-administered are not explicitly stated). All children received a booster dose of Hib-MenC-TT at the 6 year post primary series time point with 100% responding (defined as >1:8 rSBA) from each age group, although younger age groups were associated with decreased duration of protective antibody titers that were measured one year after the booster dose. [Figure 2F].

2.5 Single dose

Booy2011 [57]& 2013[58]

In a single dose study of 12-18 month old toddlers, Booy administered either dual Hib-MenC-TT vaccine or each component separate as Hib + MenC-CRM conjugate vaccines, together with the MMR vaccine to Hib primed but MenC-naïve toddlers. 99.6% (95% CI: 100-97.8%) of toddlers had SBA titers greater than 1:8 [rSBA] after 1 month in the Hib-MenC group. At 12 months, GMTs were higher in the Hib-MenC vaccine group -91.7 (95% CI: 111.3-75.6) compared to 63.8 (95% CI: 94.1-43.3), corresponding to 86.7% (95% CI: 90.7-81.9%) of children maintaining an rSBA titer >1:8 compared to 76.4% (95% CI: 84.8-66.2%) [Figure 2G]. Three years post immunization, rSBA titers ≥1:8 fell to 64.2% and 53.2% in aforementioned groups.

Figure 2.

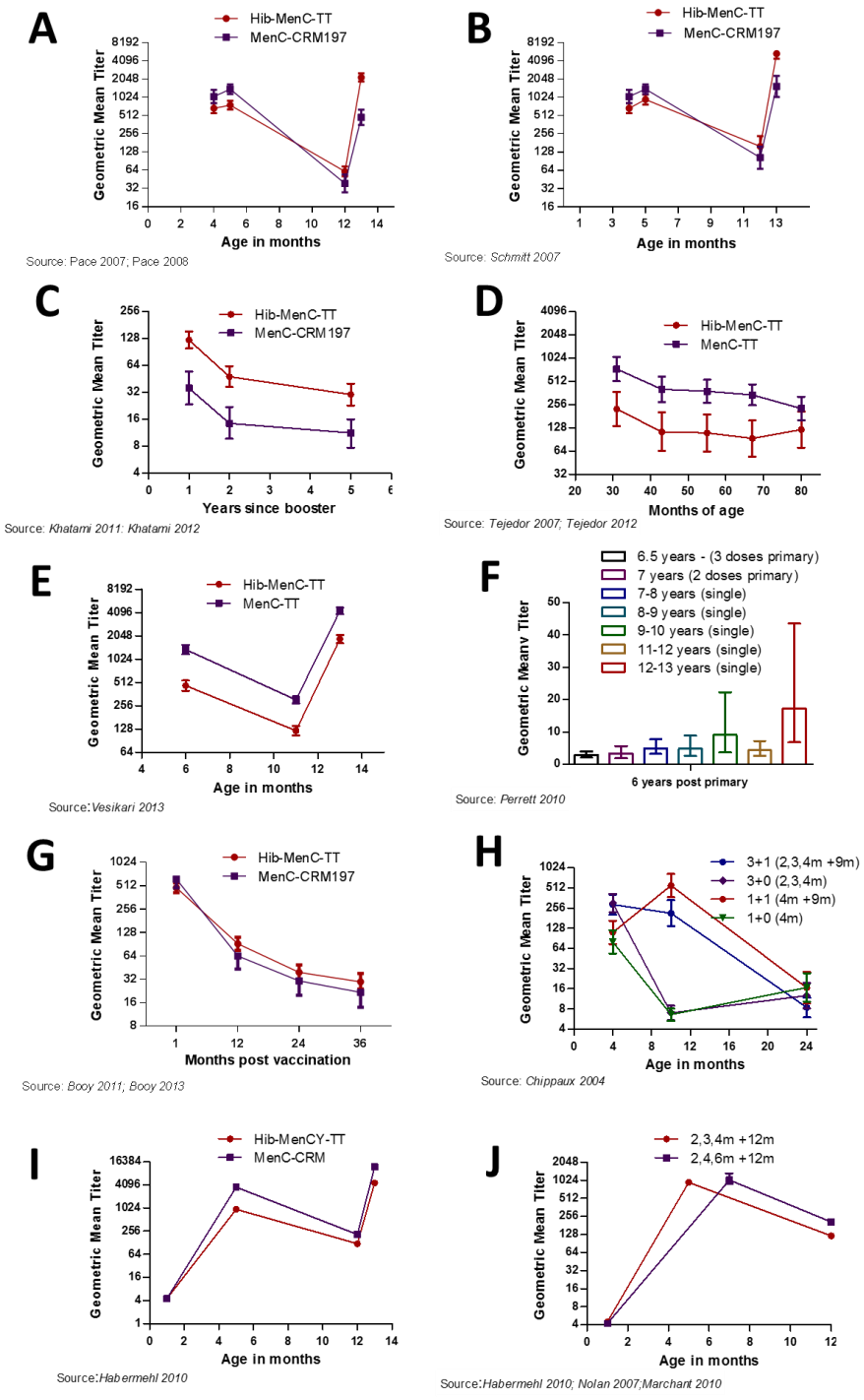

Figure Caption 2. Hib-MenC combination vaccines given in 3 or 2 dose primary series or single doses in toddlers and adolescents with long term antibody persistence. (A) 2, 3, 4 +12m and (B) 2,3,4m schedule [Pace 2007 and 2008; Schmitt 2007] (C +D) 2, 3, 4 +12 month schedule with long term antibody persistence [*Khatami 2011 and 2012; Tejedor 2007 & 2012*] (E) 3,5 and 11 month schedule [*Vesikari 2013*] (F) Multi-dose study by age group with long term antibody persistence [*Perrett 2010*] (G) Long term antibody persistence in toddlers given a single dose of combination Hib-MenC-TT or MenC-CRM197 [*Booy 2011 and 2013*].

B. Serogroup (A+C) conjugate vaccines

2.6 (3+1) 4 doses
Chippaux 2004[59] – *DT carrier protein*

In this study Chippaux vaccinated infants at 2, 3, 4 and 9 months. Anti-group C GMTs reported at 4 and 10 months were 289 (95% CI: 406-205 [rSBA]) and 215 (95% CI: 337-138 [rSBA]) respectively. These declined to 8.4 (95% CI: 11.8-6.0) at 24 months [Figure 3A]. All children were co-administered OPV and DTP at 6, 10 and 14 weeks with a 15 month booster.

2.7 (3+0) 3 doses
Chippaux 2004[59] – *DT carrier protein; Twumasi 1995[60] – CRM carrier protein*

Both studies vaccinated infants at 2, 3 and 4 month primary dose schedule. Results from Chippaux were similar at 5 months of age (after the 3rd dose) as in the 3+1 schedule above, but at 10 months GMT were substantially lower at 7.0 (95% CI: 9.0-5.4 [rSBA]) [Figure 3A]. The Twumasi study reports GMTs of 2760 (95% CI: 3291-2316 [unknown complement source]) at 5 months of age which decreased to 818 (95% CI: 1005-616) by 7 months. Children were co-administered DTP and OPV vaccines during the study.

2.8 (2+0 or 1+1) 2 doses
Chippaux 2004[59]Lakshman 2002[61] – DT carrier protein; Lieberman 1996[62] Twumasi 1995[60] – CRM carrier protein

Two studies were included using a two dose primary schedule in infants. Chippaux vaccinated at 4 months with a 9 month booster and reported GMTs at 4 months of 111 (95% CI: 166-74.4 [rSBA]) and 553 (95% CI: 821-373 [rSBA]) at 10 months of age, 1 month after the booster. GMT in this group waned considerably and comparable to other schedule in the study at 24 months, 16.6 (95% CI: 28.5-9.7 [rSBA]), which corresponds to 24.7% (95% CI: 36.1-15.3%) of those with a positive SBA at ≥1:128 serum dilution [Figure 3A]. Twusami presented an alternative schedule in infants at 2 and 6 months and strong responses at 7 months with GMTs at 1370 (95% CI: 1767-1370 [unknown complement source]). In toddlers 1.5-2 years of age, Lieberman *et al* conducted a trial using a 2 dose schedule with 2 months between doses. GMTs rose from 5 (95% CI: 6.2-4 [rSBA]) to 3197.9 (95% CI: 4491.2-2277.0 [rSBA])

at a time point of 1 month after the second dose. In a two dose regimen in adults aged 17-30, Lakshman reported GMTs increasing from 199 (95% CI: 330-120 [rSBA]) preboost to 718 (95% CI: 977-527 [rSBA]) 4-8 weeks post boost. The two doses were separated by an interval of 52-60 weeks.

2.9 Single dose studies – infants and toddlers

Chippaux 2004[59] – DT carrier protein and Twusami 1995[63] – CRM carrier protein

Single dose vaccinations at 6 months from the Twusami study were quite strong, and higher than the two dose regimen of 2 and 6 months, rising from 18 (95% CI: 25-13 [unknown complement source]) prevaccination to 2285 (95% CI: 3069-1701) at 7 month of age. Contrastingly, Chippaux dosed infants at 4 months with a comparatively modest response. GMTs in this group were reported at 79.9 (95% CI: 119-53.7 [rSBA]) at 1 month post vaccination which dropped to 6.6 (95% CI: 8.1-5.3) at 10 months and rebounding slightly to 16.8 (95% CI: 27.4-10.3 [rSBA]) at 24 months [Figure 3A].

2.10 Single dose studies – adults

Anderson 1994[64] – CRM carrier protein, Lakshman 2002[61] – DT carrier protein

In the study from Anderson, three different vaccine formulations were used: 5.5µg, 11µg and 22µg. We will only report the closest comparable vaccine formulation, 5.5ug of each PS conjugated to 48.7µg CRM197 used in the Chippaux *et al* (4µg of each PS and 48µg of DT) and Lieberman *et al* (4µg of each PS conjugated to 48µg DT) studies for consistency. In adults 18-50 years of age GMTs rose from 5 (no 95%CI available [rSBA]) to 7761. Comparatively, in the Lakshman study, GMTs rose from 36.3 (95% CI: 66.6-19.8) to 926 (95% CI: 1320-649) 4-8 weeks post immunization in adults aged 17-30.

C. Serogroup (C+Y) conjugate vaccines

2.11 (3+1) 4 doses

Habermehl 2010[65] – TT carrier protein

One study investigated the efficacy of a 3 dose primary series at 2, 3, and 4 months with a booster at 12-18 months of age with Hib combination MenC+Y vaccines. The investigators used several different vaccine formulations within the study and we only reported on the formulation closest in nature to the currently licensed Menhibrix® vaccine. Patients were co-administered DTaP-HBV-IPV, as well as and

Hib if they did not receive it as a MenC combination vaccine. All infants were above the protective titer threshold at 5 months with GMTs approximately 1030 (95% CI not available [rSBA]). Titers waned to approximately 159.3 (95% CI not available [rSBA]) before the booster dose was given, although 97.6%-90.7% remained seroprotected at this time point. Anti-Group C GMT were notably higher with the control MenC-CRM197 monovalent vaccine in this study at one month after the last primary series dose and after the booster dose [Figure 3B].

2.12 (3+0) 3 doses – TT carrier protein
Marchant 2009[66]; Nolan 2007[67]

The two studies here included regimen on a 2, 4, and 6 month primary schedule and co-administered with DTaP-IPV-HBV+PCV7. At 7 months of age, both studies report similar GMTs. Marchant *et al* reports GMTs at 1096.5 (95% CI: 1341-896.5 [rSBA]), while the Nolan study was approximately 1230 (95%CI not available [rSBA]). This correlates to 100-97% of infants seroprotected. This schedule visually presented in comparison to the Habermehl study (2, 3, 4 +12m study [Section 2.11] in Figure 3C. The Nolan study also sampled at 12 months of age with 97.4% (95% CI: 99.2-88.8%) ≥1:8 SBA and GMTs at 269 [rSBA].

Figure 3.

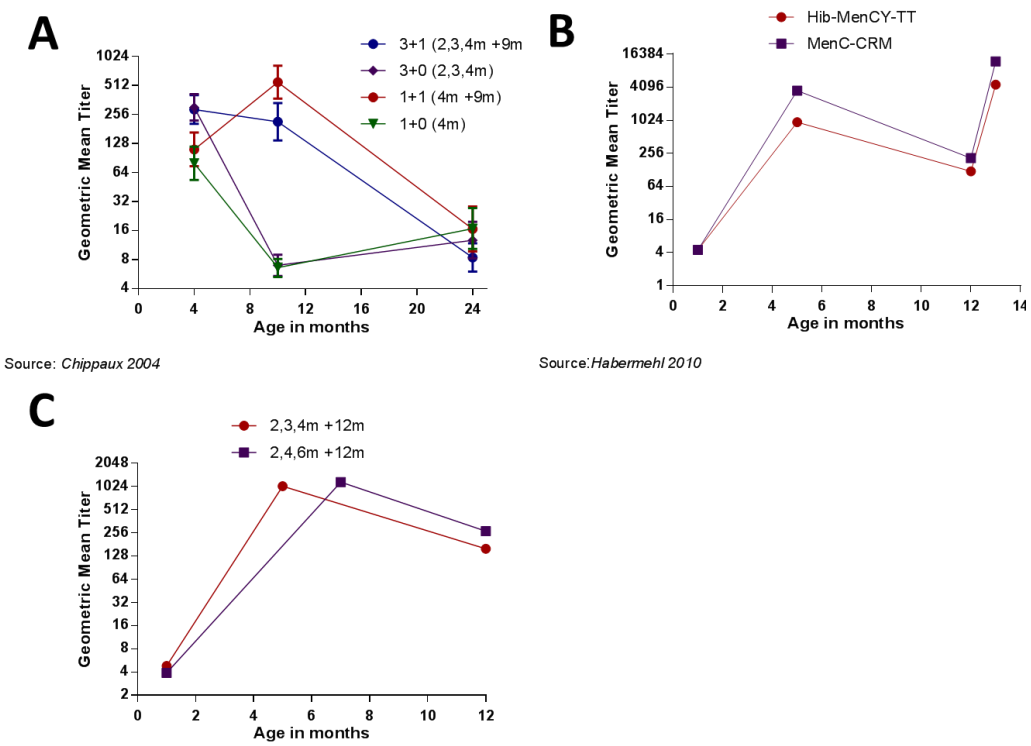

Figure Caption 3. Bivalent serogroup A+C or C+Y in combination with Hib vaccines administered as 3, 2, or 1 dose series. (A) MenA+C-DT carrier protein vaccine comparison of four primary schedules [*Chippaux 2004*] (B) Comparison of Hib-MenC+Y-TT carrier protein bivalent vaccine to MenC-CRM monovalent vaccine immunized at 2, 3, 4 +12m of age (C) Anti-GroupC GMT from Hib-MenC+Y-TT immunization with two schedules, (2, 3, 4 +12m = *Habermehl 2010*; 2, 4, 6 +12m = *Nolan 2007 & Marchant 2010*].

Author	Design	Carrier Protein	Age Group	Year Published	GRADE	Risk of Bias
Tejedor	RCT Follow-up	TT	under 1 yr	2012	2	Low
Perrett	CT	TT	under 1yr - 7 yr	2009	1	High
Khatami	RCT Follow-up	TT	0-3.5 yrs	2010	2	Low
Khatami	RCT Follow-up	TT	0-3.5 yrs	2012	2	Low
Pace	RCT	TT	12-15 months	2008	3	Low
Pace	RCT	TT	infants	2007	2	Low
Schmitt	RCT	TT	infants	2007	2	Unclear
Tejedor	RCT	TT	infants	2007	2	Unclear
Vesikari	RCT	TT	infants	2013	3	Low
Booy	RCT	TT	12-18 months	2011	2	Unclear
Nolan	RCT	TT	infants	2007	2	Unclear
Habermehl	RCT	TT	infants	2010	5	Low
Marchant	RCT	TT	infants	2010	2	Unclear
Twusani	RCT	CRM197	infants	1996	3	Unclear
Lieberman	RCT	CRM197	18-24 months	1996	3	Low
Anderson	RCT	CRM197	adults	1994	2	Unclear
Chippaux	RCT	DT	infants	2004	2	Low
Lakshman	RCT	DT	adults	2002	3	Low

Table 2A. Descriptive data table of combination Hib and bivalent A+C and C+Y vaccines included in this review.

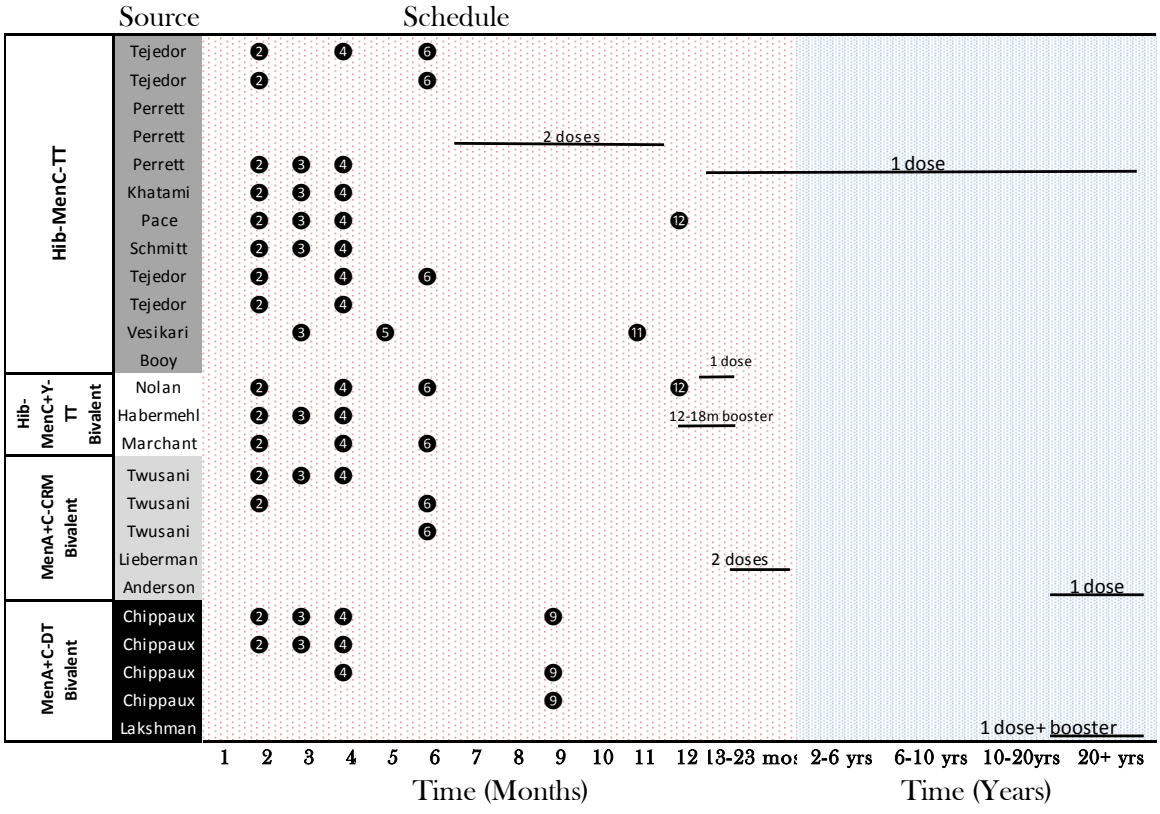

Table 2B. Visual data table of dosing schedules utilizing combination Hib and bivalent A+C and C+Y vaccines.

III. Monovalent serogroup C vaccines

3.1. 3+1 or 3+0 Schedules:

a. 2, 3, and 4 month primary series

Schmitt 2008[68]; English 2001[69]; MacLennan 2000[70]; Szenborn 2013[71]; Borrow 2003[72]; Pace 2007[49]; Pace 2008[48]; Schmitt2007 [50]; Habermehl 2010[65]

We found multiple studies using a CRM197 conjugated vaccine 3 dose primary schedule. MacLennan [10μg MenC PS and 13μg or 20μg CRM197] tested two different formulations (co-administered with DTwP-Hib-OPV) that varied in the amount of conjugated carrier protein, 13μ or 20μg. The 20μg group was more immunogenic overall, and at five months of age GMTs rose to 629 (95% CI: 857-462 [rSBA]). At the same time point, Schmitt (Meningitec™; DTaP-HBV-IPV) reports GMTs at 1400.7 (95% CI: 1683.5-1165.4 [rSBA]), English reported (10ug MenC PS & 25μg CRM, 0.5mg $AlPO_3$; DTwP) at 1429 (95% CI: 1814-1125 [rSBA]), Pace (Meningitec™; DTaP-HBV-Hib) at 1002.6 (95% CI: 1205.6-833.8 [rSBA]). Schmitt published two studies in which a monovalent CRM197 vaccine was given at 2, 3, and 4 months, yet with varying vaccine formulations and laboratory assays [73, 74]. The two studies reported 100% of subjects above defined antibody SBA titers after the primary series, however 80.2% (95% CI: 87.8-70.6%) and 89% (95% CI: 94-89%) reported seroprotective at 12 months. GMTs carried out to 12 months of age fell to 104 (95% CI: 158.3-68.4 [rSBA]), 24 (95% CI: 34-17 [rSBA]) in the MacLennan study, and 38.6 (95% CI: 54.2-27.5 [rSBA]) in the Pace study **[**Figure 4a]. MacLennan and Pace is the only study to boost at 12 months of age resulting in a 113 fold and 12 fold increase in GMT sampled after one month respectively, although the whole cell pertussis vaccine has been shown to augment MenC immune responses which may account for the log difference.

Two studies on a 2, 3, and 4 month primary schedule investigated TT protein carrier formulations, although one was administered as a heptavalent DTaP-HBV-IPV/Hib/MenC-TT vaccine. Using the heptavalent vaccine formulation, Szenborn reported 98.4% (95% CI: 99.8-94.4%) and a GMT of 786.9 (95% CI: 971.9-637.2 [rSBA]) at 5 months of age. With an individual monovalent TT vaccine, Borrow (DTwP/Hib co-administered) reported GMTs at 1405.2 (95% CI: 1696.1-1164.2 [rSBA]), and Schmitt (DTaP-HBV-IPV) at 1008.2 (95% CI: 1267.3-802.0 [rSBA]) at 5 months of age. As before,

antibody titers waned over 8-10 months although the heptavalent vaccine maintained higher overall GMTs 148.8 (95% CI: 193.5-114.4) compared to the monovalent vaccine 21.5 (95%CI 29.2-15.8 [rSBA]) (Borrow) and 189.1 (95% CI: 287.3-124.5 [rSBA]) (Schmitt) [Figure 4b]. This corresponds to 88-70% seroprotected, and response to either a booster dose or polysaccharide challenge was strong and roughly equivalent.

b. 2, 4, and 6 month primary series

*Tejedor 2007[53] & 2006[75] & 2004[76]; Halperin 2002[77]; Diez-Domingo 2009[78]; Nolan[67]***.** All six studies using a 2, 4, and 6 month primary schedule were CRM197 conjugated vaccines. Two of these studies included a booster dose at 14-18 months. The vaccine formulations were the similar in all four studies except the Halperin study in which 25µg of CRM197 was conjugated to oligosaccharide as opposed to 15µg used in the others. Two studies from Tejedor (co-administered DTaP-HBV-IPV/Hib) using this schedule reported GMTs at 7 months of age at 1033 (95% CI: 1221-875 [rSBA]) 1833.7 (95% CI: 2251-1493 [rSBA]), and approximately 2010 [rSBA] (Nolan). Contrastingly in the Halperin (DTaP-IPV-Hib co-administered) study GMTs were reported at 232 (95% CI: 260-207 [rSBA]), although 98%-100% were above the protective level for antibody titers at this time point in all the studies mentioned prior. Halperin administered a booster dose at 14-18 months of age. Pre-boost seroprotection ranged from 74% (95% CI: 81-66%); GMT= 20, 24-17 95%CI [rSBA]) with strong immune responses 1 month after the booster (95% CI: GMT=1344, 1506-1199).

c. 3, 4, and 5 months or 3, 5, and 7 month primary schedules

Tejedor 2004[76]; Sigurdardottir 2007[79]

Sigurdardottir investigated a CRM197 conjugate vaccine on a 3, 4, and 5 month primary schedule (co-administered with DTaP-IPV/Hib+PCV9) with a booster at 12 months (with 23VPPS). 93% of subjects had ≥1:128 positive SBA titers [unknown complement source] at 6 months of age (GMT=564, 95% CI: 807-394 [rSBA]). The booster dose response against serogroup C polysaccharide was 2.2 times stronger when administered with a 23-valent pneumococcal vaccine than with the 9-valent formulation. Tejedor's comparison group to the study mentioned in section 3.2 vaccinated at 3, 5 and 7 months was

roughly equivalent after 2 doses compared to the 2, 4 and 6 month schedule in terms of GMTs, with 100% seroprotected at 8 months of age(GMT=2257.1, 95% CI: 2593.5-1964.4 [rSBA) [Figure 4c].

3.2. 2+1 or 2+0 Schedules

a. 2 and 3 months, or 2 and 4 months primary schedules

Southern 2009[80]; Poellabauer 2013[81]; Borrow 2003[72]; Tejedor 2007[53] & 2006[75]; Schmitt 2008[68]; Diez-Domingo 2013[82]; Snape[24].

Two studies, Diez-Domingo and Schmitt, administered only a CRM197 conjugate vaccine and Southern compared both a TT and CRM197 conjugate vaccine, while Snape administered only a TT conjugate vaccine at 2 and 4 months (all four studies co-administered DTaP-IPV/Hib). Diez-Domingo compared co-administration with either 13 or 7 valent pneumococcal vaccines. In both groups, 97-99% of subjects measured ≥1:8 positive rSBA at 5 months of age. Here, co-administration with the lower 7 valent pneumococcal vaccine appeared to be illicit higher GMTs; PCV7 GMT, 730.8 (95% CI: 832-642 [rSBA]) compared to PCV 13 432.3 (95% CI: 517-361 [rSBA]). Schmitt reported GMTs at 337 (95% CI: 437-260 [hSBA]) at 5 months of age, corresponding to 98% (95% CI: 100-93%) >1:8 hSBA, nearly identical numbers from Snape (GMT = 339 (95% CI: 551-209 [hSBA]) which waned to 89% (95% CI: 94-89%) >1:4 positive hSBA at 12 months of age (GMT=34, 95% CI: 47-24 [hSBA]). Southern compared the three different licensed Meningicoccal serogroup C conjugate vaccines, Neis-Vac-C®, Meningitec®, and Menjugate®, the latter two being CRM197 conjugates while Neis-Vac-C® is a TT conjugate formulation. The TT conjugate subjects responded strongly after one dose, at three months of age GMTs were 295 (95% CI: 438-195 [rSBA]) with 97% seroprotected compared to 53% and 80% in the CRM197 groups (GMT=10 and 48 respectively [rSBA]). However, after the second dose at 5 months of age nearly all subjects were seroprotected (95% CI: 100-96%). Subjects vaccinated with Menjugate® measured the highest GMT, 702 (95% CI: 875-563) at this time point [Figure 4d].

Four studies reported on TT conjugate vaccines at 2 and 4 months, all of which were equivalent formulations. Tejedor (concomitant vaccines: DTaP-HBV-IPV/Hib) reported GMTs at 5 months of age from two groups, one given HBV vaccine at birth and one without. The HBV co-administered group had higher GMTs (1542, 95% CI: 1856-1282 [rSBA]) although 100% were seroprotected in both groups. Borrow (DTwP/Hib) reported similar GMTs at 5 months, 1325.5 (95% CI: 1575.1-1115.4 [rSBA]),

which waned to 20.7 (95% CI: 29.4-14.6 [rSBA]) at 14 months of age. Poellabauer (concomitant vaccines DTaP-IPV-HBV/Hib+PCV13) reported GMTs at five months at 624.1 (95% CI: 685.5-568.2 [rSBA]), corresponding to similar GMTs with the study from Southern, 427 (95% CI: 564-323 [rSBA]). By 12 months of age this reduced to 29.5 (95% CI: 35.7-24.4) with 67.8% (95% CI: 72.7-62.5%) ≥8 positive rSBA titers. 1 month after a booster dose at 12 months of age 99.6% were seroprotected (GMT=1538, 95% CI: 1712-1381).

One study immunized at 2 and 3 months. Southern again compared the three licensed monovalent vaccines at 3 months of age, before the second dose, and then again at 4 months of age after the second dose. As in the 2, 4 month schedule mentioned above, nearly all subjects had protective titers 100-98% at 4 months, and the CRM197 vaccine, Menjugate® resulted in the highest GMT (648, 95% CI: 1060-397 [rSBA]) of the three vaccines [Figure 4d].

b. 2 and 6 months, or 3 and 5 months primary schedules

Vesikari 2013[55] & 2011[83]; Diez-Domingo 2009[78]; Sigurdardotti 2008[79]; Wysocki 2010[84].

Two studies immunized at 2 and 6 months, one with a CRM197 vaccine and one using a TT conjugate. Both of these boosted at 12-18 months. Wysocki compared the immune responses with or without the co-administration of PCV7. Concomitant administration of PCV7 (as well as DTaP-HBV-IPV/Hib in both groups) did not have a substantial influence the immune response to meningococcal vaccination. At 7 months of age GMTs were 376.5 (95% CI: 428.5-330.7 [rSBA]) which decreased to 23.8 (95% CI: 29.3-19.3 [rSBA]) just before the booster at 12 month of age. Diez-Domingo only reported the post-boost GMT around 14-18 months and compared the differential immunogenicity of carrier protein used for priming, either CRM197 (3 doses priming) or TT (2 doses priming). Priming with the TT conjugate vaccine and boosting with either a TT or CRM197 conjugate vaccine was roughly equivalent (GMT=6786, 95% CI: 9167-6786; and 6278, 95% CI: 8144-4841; respectively). This is compared to titers from priming with only CRM197 conjugates which were 3.5 times lower, GMT=1746 (95% CI: 2213-1378) [Diez- Domingo] (Figure 4e) , also reported after a 12 month booster from Wysocki at 713.9 (95% CI: 893.2-570.5).

Two studies used a 3 and 5 month primary schedule, one with CRM197 protein carrier conjugated and on with TT. Vesikari a compared TT conjugated MenC vaccine on this schedule with the co-administration of rotavirus vaccine (Rotateq®) along with DTaP-HBV-IPV, or non-co-administration of Rotateq®. Co-administration was non-inferior and at six months of age 100-95.6% of subjects were seroprotected (GMT=1457.8, 95% CI: 1698.2-1251.2 [rSBA]) in the concomitant group. This agrees with another study from Vesikari that reports GMT at 1362 (95% CI: 1561-1189 [rSBA]) at six months, which declined to 304 (95% CI: 337-274) at 11 months just before a booster dose, although 100% of subjects were still above the 1:8 titer threshold considered protective. Sigurdardottir vaccinated at 3 and 5 months with a 12 month booster dose (co-administered with DTaP-IPV/Hib+PCV9 or PCV23). The CRM197 vaccine resulted in 87.5% (95% CI: 94.8-75.9%) seroprotected at six months of age. The booster dose was co-administered with either 9 or 23 valent pneumococcal vaccine. As seen before, the 23 valent pneumococcal increased the immunogenicity of the booster when comparing GMTs (2623, 95% CI: 4313-1595; and 1928, 95% CI: 3160-1176 [rSBA]).

c. 2 doses in toddlers
MacDonald 1998[85]

Two doses two months apart with a CRM197 monovalent conjugate vaccine was immunogenic in toddlers 15-23 months old. 2 months after the first dose 90% (95% CI: 97-79%) had rSBA titers ≥1:8, while after the second dose this rose to 98% (95% CI: 100-88%).

3.3 Single Dose schedules
a. Single dose or (1+1) in infants less than 12 months
Borrow 2003[72]; Poellabauer 2013[81]; Findlow 2012[86] Pace 2008[87]

The three studies included here all employed the equivalent formulations of the TT conjugate vaccine although one compares it to a licensed CRM197 conjugate vaccine. In a single dose comparison group from Borrow (DTwP/Hib), vaccination at 2 months of age resulted in GMTs of 460.2 (95% CI: 574-369 [rSBA]) after one month. Titers waned to 10.4 (95% CI: 14.3-7.5) at 12 months of age, corresponding to 43.8% with rSBA titers ≥1:8. Poellabauer (DTaP-IPV-HBV/Hib+PCV13 co-administration) performed single vaccinations at 4 months, and at 6 months of age. Both schedules were

roughly equivalent at 1 month post vaccination, however, just prior to a booster dose at 12-23 months of age, those immunized at 4 months were less likely to remain protected, 78% (95% CI: 82.2-73.4%) compared to 90.7% (95% CI: 93.5-87.2%) for those immunized at 6 months. Although after the booster dose, GMTs were higher in the group immunized at 4 months, 2472 (95% CI: 2745-2226 [rSBA]) compared to 1875 (95% CI: 2086-1684 [rSBA]).

Findlow compared a single dose of either the licensed TT (Neis-Vac-C®) or CRM197 (Menjugate®) vaccine when administered at 3 months of age with DTaP-IPV-Hib and PCV7. 1 month post boost the TT conjugate resulted in higher GMTs, 223.3 (95% CI: 306.1-162.9) compared to 95.8 (95% CI: 138.2-66.4) from the CRM conjugate. Just before the booster dose at 12 months of age, regardless of which vaccine was given, subjects maintained GMTs between 4.2 and 5.2 (95% CI: 7.7-2.9 combined), corresponding to 28-24% with positive rSBA >1:8 [Figure 4f]. Responses to the booster were more robust in the TT vaccinated subjects (GMT=2259 compared to 355.9). Pace also investigated single dose schedules of CRM and TT conjugates given at 3 months of age as compared to 2 doses at 3 and 4 months of age. At 12 months of age 26% in the single dose CRM group and 40% in the single dose TT conjugate group had MenC rSBA >1:8 compared to 41% in the two dose CRM group. A Hib-MenC-TT conjugate was administered at 12 months to all groups and 1 year later 84% of children primed with a TT conjugate had MenC rSBA >1:8 compared to 31-20% of those primed with a CRM conjugate vaccine.

b. Single dose in toddlers 12-23 months of age
Szenborn 2013[71]; Vesikari 2012[43]; Knuf 2012 [42]; Booy 2011[57] & 2013 [58]

At 12-18 months of age Szenborn vaccinated with a single dose of a TT conjugate vaccine to infants previously administered DTaP-HBV-IPV/Hib+PCV10. GMTs rose from 5.4 (95% CI: 6.6-4.5 [rSBA]) prevaccination to 2320.4 (95% CI: 2638.8-2040.3 [rSBA]) 1 month post vaccination corresponding to 100% (95% CI: 100-96.8%) of toddlers with ≥1:8 rSBA titers post immunization. Vesikari and Booy published a study with a monovalent CRM197 comparison group and followed antibody persistence up to three years after single dose priming in toddlers 12-23 months [Figure 4g]. As expected, antibody titers waned considerably after the first year from 415 (95% CI: 580-270 [rSBA]) and 621 (95% CI:

480-303 [rSBA] one month post vaccination to 77.1 (95% CI: 121.1-49.1 [rSBA]) and 63.8 (95% CI: 94.1-43.3); Vesikari and Booy respectively. In the second year antibody waning was reduced considerably only decreasing to 57.7 (95% CI: 99.3-33.5) which interestingly tripled when measured at year 3 in the Vesikari study. Knuf reported that toddlers 12-14 months given a CRM197 single dose had a GMT of approximately 28 after 15 months, although their GMT 1 month post vaccination was nearly identical to Vesikari and Booy.

Figure 4.

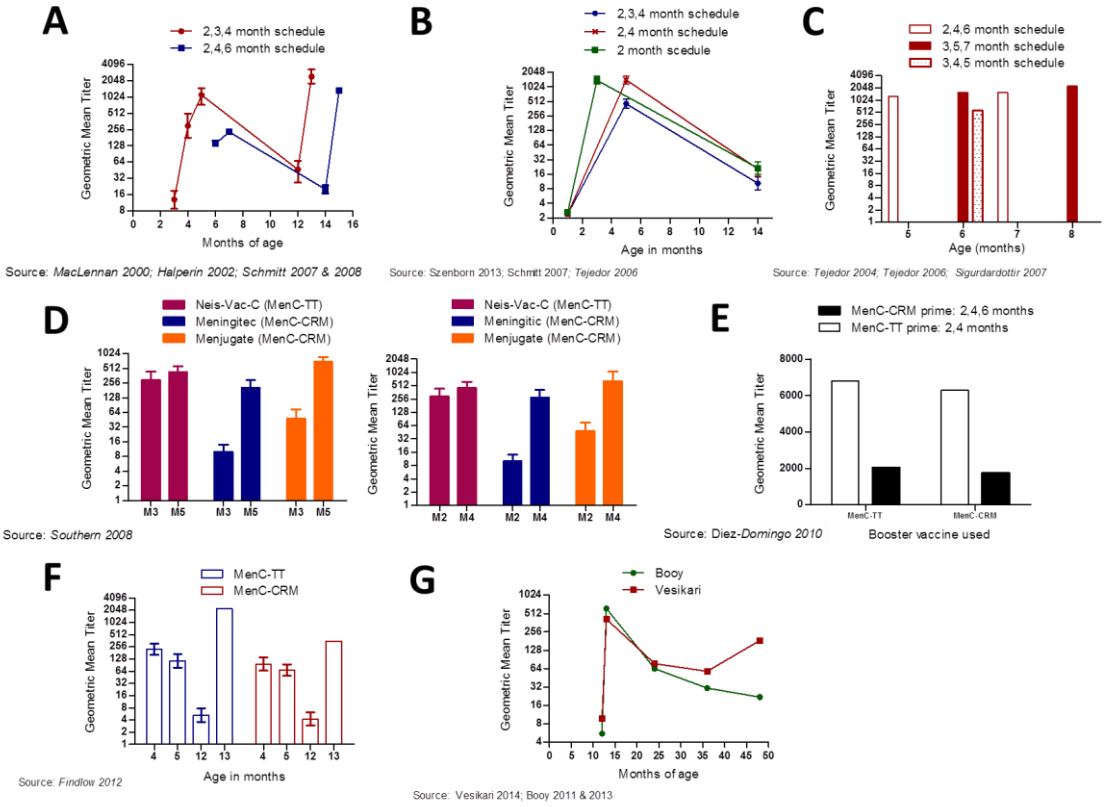

Figure Caption 4. Monovalent MenC vaccine immunogenicity utilizing TT or CRM carrier proteins with long term antibody persistence and multiple dosing strategies. (A) CRM conjugate vaccines with a 2,4,6 or 2,3,4 month primary schedule [*MacLennan 2000; Halperin 2002; Schmitt 2007 & 2008*] (B) TT conjugate vaccines with 1,2, or 3 doses in infancy [*Szenborn 2013; Schmitt 2007; Tejedor 2006*] (C)CRM conjugate vaccine comparing 2,4,6 month primary schedule to 3,5,7 month series [*Tejedor 2004 & 2006; Sigurdardottir 2007*] (D) CRM conjugate 2 dose primary series at 2,4 months or 2,3 months using 3 licensed serogroup C vaccines [*Southern 2008*] (E) Comparison 14-18 month old children given either (1) MenC-TT 2 dose primary series at 2,4 months or (2) MenC-CRM 3 dose primary series at 2,4,6 months when given a booster dose with either vaccine in the second year of life [*Diez-Domingo 2010*] (F) Comparison of a single dose of MenC-TT or MenC-CRM at 3 months of age with a 12 month Hib-MenC-TT booster [*Findlow 2012*] (G) Two studies investigating long term antibody persistence after 12-18 month old children received one dose of MenC-CRM [*Vesikari 2014; Booy 2011 & 2013*].

c. Single dose in children, adolescents, and young adults

Khatami 2011[88]; Sakou 2009[89]; Whalley[90, 91]; Snape[92, 93]; Perrett[94]

All of the studies included in this section reported long term antibody persistence after single dose priming in ages ranging 1-20 years. Khatami followed a single cohort over 10 years after vaccinating with a CRM197 vaccine between the ages of 1-4. Seroprotective antibody titers had fallen to 28.9% (95% CI: 32.1-25.6%) after approximately 2 years and to 15.3% (95% CI: 18.9-11.7%) after approximately 10 years from vaccination (current age ~12.2 years). Sakou followed a cohort of three different age groups after immunization with either Neis-Vac-C® or Menjugate® at the approximate ages of 1-14 years. 5 years after immunization, subjects immunized after the age of 10 maintained seroprotective antibody titers better than their younger counterparts [Figure 5a]. The group which was over 10 years of age at immunization remained 62.2% (95% CI: 76.4-48.1%) seroprotected (>1:8 rSBA) compared to 37.8% (95% CI: 48.3-27.3%) in 6-10 year olds, and 14.1% (95% CI: 19.8-8.4%) in those under 6 years of age at the time of vaccination.

Whalley reported over two studies from a trial in which subjects aged 9-12 years who were previously vaccinated with a CRM197 vaccine were given a booster dose at the ages of 13-15. Before the booster dose, median time of 3.8 years, GMTs remained at 153 (95% CI: 298-79 [rSBA]). Immune responses to the booster dose were robust and after 6.20-7.04 years GMTs remained high at 1373 (95% CI: 1977-954 [rSBA]) corresponding to 100% of 26 subjects with ≥1:8 rSBA titers. Interestingly, nearly 7 years after original priming, the control group which received no booster still had GMTs of 284 (95% CI: 483-167 [rSBA]) [Figure 5b].

Two studies from Snape also investigate long term antibody persistence in adolescents and teenagers originally primed with either one of three licensed MenC monovalent vaccines or Menjugate® MenC-CRM only. Individuals immunized between the ages of 6-15 years were sampled again after 5 years. Older age at vaccination correlated here again with higher sustained GMTs [Figure 5c]. Of those immunized with Menjugate® at the age of 6-8 years, 76.4% (95% CI: 81.2-70.9%) retained seroprotective antibody titers. This increased to 88.2% (95% CI: 93.1-81.6%) for those aged 12-15 years at the time of immunization. In an antibody kinetics study, Snape also reported a baseline of 75% of subjects with ≥1:8 hSBA after a mean time of 3.7 years since immunization of 13-15 year

olds, correlating with the aforementioned study. A separate but complementary study from Perrett also looked at a cohort originally vaccinated with one of the three licensed MenC monovalent vaccines 7-8 years after a single catch-up immunization in adolescents. They also found a positive correlation with long term antibody persistence and older age at immunization. The oldest children at 6-8 years of age when given their first MenC immunization were much more likely to maintain protective antibody titers after 7 years.

d. Single doses in adults

Southern 2004[95]; Richmond 2000[96, 97]; Goldblatt 2002[98]

All three studies compared adults who had previously received a meningococcal polysaccharide vaccine with those who were vaccine naïve. Two of the studies used a CRM197 protein carrier conjugate vaccine and one used a TT conjugate vaccine. All three studies reported higher GMTs with vaccine naïve subjects as compared to those who had previously been vaccinated with a plain polysaccharide meningococcal vaccine. Reported GMTs after vaccine naïve subjects were immunized with a CRM197 conjugate were 734.6 (95% CI: 1137-474 [rSBA]), which declined modestly to 637.3 (95% CI: 1122.2-361.9 [rSBA]) (Goldblatt) after six months, and 1336 (95% CI: 1966-908 [rSBA]) (Richmond). This same group immunized with the TT conjugate had GMTs at 1757 (95% CI: 2803-1102), which after six months declined to 1625.5 (95% CI: 2383-1108 [rSBA]) (Southern).

Figure 5.

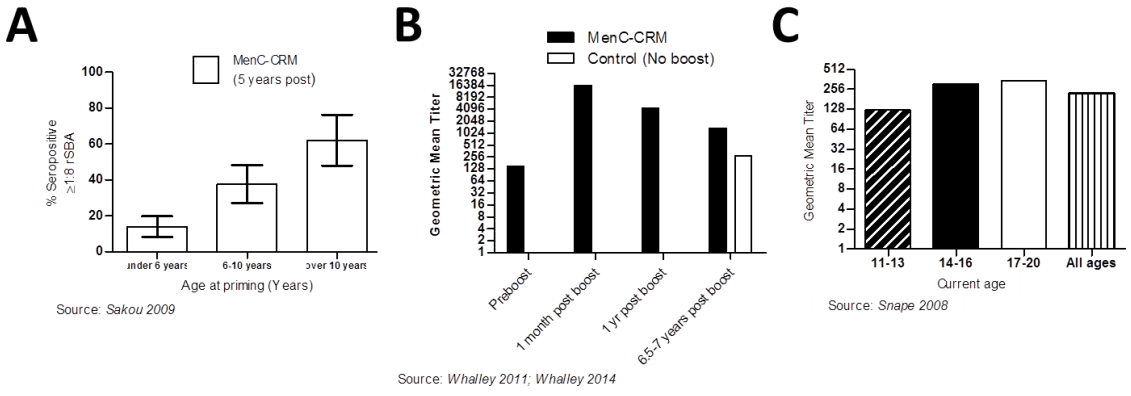

Figure Caption 5. Long term antibody persistence after a single dose in children and adults with CRM carrier monovalent formulations. (A) Age at which single dose was administered that maintained ≥1:8 rSBA titers *[Sakou 2009]*. (B) GMT over 7 years after adolescents 9-20 years of age were immunized with a single MenC-CRM dose [*Whalley 2011 & 2014*] (C) Five years post single dose by current age (CRM vaccine only) [Snape 2008]

Author	Design	Carrier Protein	Age Group	Year Published	GRADE	Risk of Bias
MacDonald	RCT	CRM197	15-23 months	1998	4	Low
Schmitt	RCT	CRM197	infants	2008	3	Low
English	RCT	CRM197	infants	2000	5	Low
MacLennan	RCT	CRM197	infants	2000	5	Low
Diez-Domingo	RCT	CRM197	infants and toddlers	2013	3	Low
Tejedor	RCT	CRM197	infants	2006	2	Unclear
Halperin	RCT	CRM197	infants	2002	5	Low
Tejedor	RCT	CRM197	infants	2004	2	Unclear
Domingo	RCT	CRM197	14-18 months	2010	3	Low
Wysocki	RCT	CRM197	infants	2010	3	Low
Sigurdardottir	RCT	CRM197	infants	2007	2	Unclear
Richmond	RCT	CRM197	adults	2000	2	Unclear
Goldblatt	RCT	CRM197	adults	2002	1	Unclear
Snape	Cohort	CRM197	9-20 yrs	2008	0	Unclear
Khatami	Cohort	CRM197	1-4 yrs	2011	0	Low
Whalley	Cohort	CRM197	9-20 yrs	2014	3	Low
Whalley	Cohort	CRM197	9-20 yrs	2011	3	Low
Snape	Cohort	CRM197	10-12 yrs	2006	3	Low
Perrett	Cohort	CRM197	2-8 yrs	2015	0	Unclear
Pace	RCT	CRM197	infants	2015	2	Low
Southern	RCT	TT	infants	2008	3	Low
Szenborn	RCT	TT	infants	2013	3	Low
Borrow	RCT	TT	infants	2003	3	Low
Poellabauer	RCT	TT	infants	2013	1	Low
Findlow	RCT	TT	infants	2012	3	Low
Vesikari	RCT	TT	infants	2011	2	Unclear
Southern	CT	TT	adults	2004	1	High
Sakou	Cross-sectional	TT	1-14 yrs	2009	0	Unclear

Table 3A. Descriptive data table of monovalent serogroup C vaccine studies included in this review.

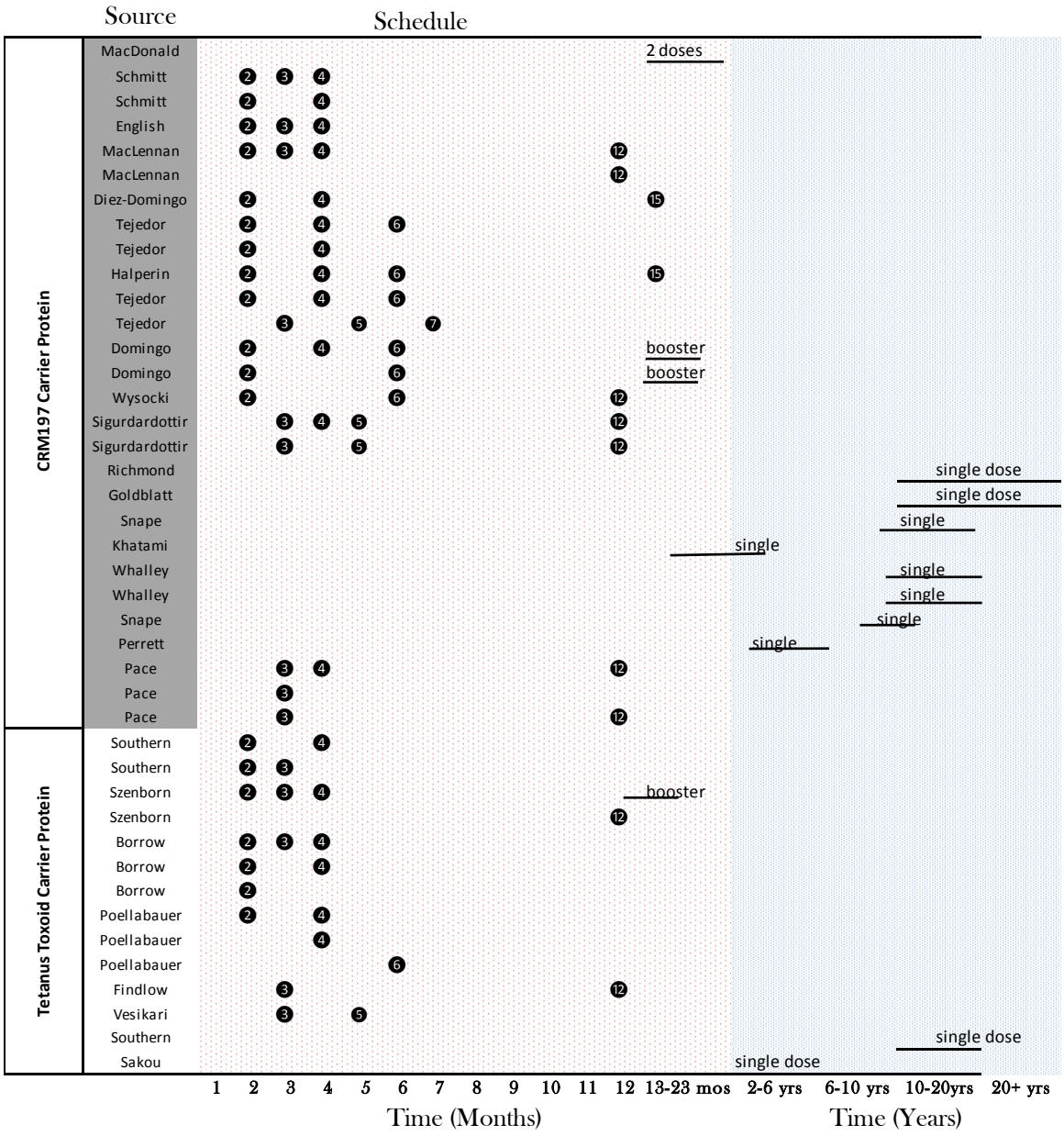

Table 3B. Visual data table of included studies where monovalent serogroup C vaccines are the primary comparison group.

Chapter 5
Discussion

Summary

Our review included 63 studies which evaluated the effectiveness of N. Meningitidis Serogroup C containing conjugate vaccines on the basis of their immunogenicity. No clinical trials on clinical efficacy are available, nor are they feasible due to the low incidence of disease. The included studies were matched for comparison based on their primary vaccine under investigation, dosing schedule, and age group. Even though these matched studies shared many important characteristics, there remains a high degree of heterogeneity between vaccine formulations, which may not have been explicitly stated in the original study, including the exact serogroup C polysaccharide and carrier protein concentration, the addition of adjuvants and their composition, as well as the laboratory methods including the definition of positive serum bactericidal assay and source of complement component used. All of these components influenced reported GMT and the percent of those considered protected. This is extremely apparent in well matched studies that reported highly contrasting outcomes. Therefore, only studies that were similar in vaccine schedule, formulation and serum complement source were combined into figure panels however they are provided as visual references and not with statistical inference as a true meta-analysis.

A. Quadrivalent vaccines

In infant series we only have studies using the CRM conjugated vaccine. Regardless of the schedule, when administering multiple doses before 12 months of age, protective antibody titers were only retained in 40-70% of subjects by 12 months of age. However, this was less apparent when administering a single dose at 6 months of age which maintained protective titers in 86% of children at 12 months. In multi-dose studies during primary series, the largest decrease in antibody titer happened rapidly, within 3 to 4 months after the primary series was administered. Boosting at 12 or after months of age was strongly immunogenic in all primary schedules used.

Single dose vaccines were well tolerated and strongly immunogenic in young children and adults older than 12 months, although immune responses were quite variable between the three protein carriers. DT and CRM conjugates reported lower percentages of subjects above the defined threshold

for short term protection with 54%-64% of 11-18 year olds that maintained GMT >1:8 rSBA at 3 years post vaccination, whereas TT conjugated quadrivalent vaccines induced strong antibody persistence in all age groups with 90-98% of those aged 1-25 retained protective titers after 3 years, which emphasized how antibody persistence needed for protection is critically dependent on the type of protein carrier or vaccine used. This correlated with age at priming, as those 11 years and older were more likely to maintain protective titers long term compared to younger children. Previous studies have also shown that immune responses in subjects who received quadrivalent polysaccharide vaccine and then given a single dose of quadrivalent conjugate vaccine may rescue immuno hyporesponsiveness and result in avidity maturation as well as higher or non-inferior post-boost GMTs compared to MenC naïve controls [18, 19, 99, 100].

B. Bivalent and Hib Containing Vaccines

Three doses compared to 2 or fewer doses in infancy were also non-inferior with bivalent (A+C) and (C+Y) vaccines. The bivalent Hib conjugates were yielded higher overall GMTs than the plain A+C bivalent vaccines, although this may be a carrier protein effect. Hib-MenC+Y is conjugated to tetanus toxoid, which has been shown to illicit stronger immune responses with equivalent meningococcal vaccines compared to other protein carriers here, as well as in several previous studies[101],[57],[102],[103].

Monovalent dual Hib-MenC-TT vaccine induced long term antibody persistence that resulted in a higher percentage of infants with GMTs >1:8 when immunized later at 2, 4, and 6 months during infancy compared to 2, 3, and 4 months (66-52% compared to 92-68% respectively at 5 years post immunization). Hib-MenC-TT vaccines also maintained higher GMTs as compared than a monovalent CRM conjugated as we have seen before. Overall waning was marginally decreased with Hib-MenC combined vaccines during infancy, although they were shown to be slightly inferior to monovalent TT conjugated equivalents. Single doses of Hib-MenC combination vaccines were also highly immunogenic after one year of age and persisted in approximately 70-58% of children at three years post vaccination.

C. Monovalent Vaccines

The more pronounced differences from later schedules in infancy were less dramatic with monovalent group C vaccines. Schedules of 2, 3, and 4 months were roughly equivalent to 2, 4, 6 months, although the latter were only studied with CRM carrier vaccines and this may be a reflection of the carrier protein. At 12 months of age after the primary series, CRM or TT carrier vaccines had similar percentages of children above the defined threshold of protection, ranging from 60-89%. Although it is well established that antibody titers decrease as much as 90% in the first year after infant primary series with MenC conjugate vaccines, protection is estimated at 40-50% for 2-3 years following the last dose before 12 months of age [104]. CRM containing vaccines consistently show a diminished response one month after a dose at 2 months, compared to TT conjugate vaccines at this time point. Additional doses in infancy, 3 compared to 2 or even 1 dose, were non-superior at 12 months of age when comparing GMTs and percentages of children still considered protected [103, 105, 106]. Multiple studies from the UK have shown that a single dose is sufficient to provide protection until a booster dose at 12 months which resulted in a decreased primary series to a single dose in the first year of life[107]. Additionally, several studies have shown that the initial dose of TT conjugates to be more immunogenic than CRM equivalents as well as when given in fewer doses, or when only used as the priming dose [108]. Although it is critical that the priming vaccine is a protein conjugate, the responses in many studies using polysaccharide challenge or booster doses were comparable to protein conjugates and more research is needed to determine if this is an cost-effective alternative for boosting[96, 109, 110]. Long term antibody persistence in our review was only shown with single doses CRM vaccines administered after one year of age. Single doses in toddlers 12-23 months of age were well tolerated and persistent seroprotective titers were maintained in 50-70% of children for 2-3 years following immunization [44, 57, 58, 111]. As in quadrivalent and Hib containing MenC vaccines, older age correlates with longevity of protective titers. Approximately 93-70% of adolescents above the age of 10 retain ≥1:8 rSBA after 5 years, while those under the age of 10 range from 37-14% seroprotected 5 years post-immunization to 19-12% after 10 years.

D. Public Health Implications

There are multiple public health benefits of optimizing a dosing regimen. First we should consider the cost of vaccination to the government, private physician or insurance company. The current listed price for the cost of one dose of a quadrivalent serogroup ACWY meningococcal vaccine is approximately $115 USD to the private sector in the USA. Hypothetically, if the US inoculated 4 million people with the quadrivalent vaccine each year the cost of the vaccine per dose reaches up to $500 million USD. Eliminating an unnecessary dose would of course save a tremendous amount of money on vaccine costs but alternatively recognizing that another dose was necessary to prevent $500 million in health care expenditures would be equally advantageous. The ideal situation is a vaccine that protects 100% of people for life with a single dose. Unfortunately this is very rarely the case, and another unwanted side effect of multiple dosing schedules is lower patient compliance. By removing unnecessary doses of vaccine from a countries schedule we can positively impact patient acceptance. Additionally, we may reduce the number of trips to see a physician which can be especially important in low and middle income countries where patients may traverse long distances to see a doctor.

Meningococcal meningitis can occur rapidly after acquiring the bacteria and protection against disease is associated with the level of circulating antibodies. The long term window of protection that we can expect after vaccination is therefore critically important for determining appropriate boosting recommendations. Our review includes all available data on long term circulating antibodies that may better inform vaccine policy makers on the best practices for their country based on disease prevalence to reduce transmission and incidence rates of this potentially fatal pathogen.

E. Strengths and Limitations

To our knowledge this is the first systematic review comparing the various schedules of monovalent, bivalent and quadrivalent meningococcal group C vaccines. Previous reviews have compared dosing regimens between polysaccharide monovalent and multivalent vaccines as well as several monovalent conjugate vaccines <<insert refs>>. This review builds on this information and incorporates recent clinical trials and long-term follow-up studies to include the multivalent and combination Hib conjugate vaccines. A major strength of this study is a comprehensive assessment of the long term window of protection across age groups. Additionally this is the first review to compare

not only the protein carrier in conjugate vaccines but the immunogenicity of the monovalent to multivalent vaccines. Due to the heterogeneity across studies with respect to laboratory assays, reagents used, and formulations of the vaccine that were sometimes not explicitly stated in the studies, we were not able to conduct meta-analysis . The figures that we compiled attempt to visually represent very similar studies with consistent results but are not meant to draw conclusions. Another serious limitation is the lack of a two-judge review procedure for the inclusion and exclusion of studies. This may not only introduce researcher bias, and attempts will be made to address it in future.

F. Gaps in Evidence

Our search strategy failed to identify any multi-dose primary series studies on quadrivalent vaccines other than CRM197 protein conjugates. Long term follow-up studies will also be needed for multi-dose primary series vaccinations with quadrivalent vaccines as well as additional studies on long term follow-up in young children and adults after single or boosting dosing. Due to the low incidence rates of disease, clinical effectiveness studies are not feasible. Additional data on vaccine impact are needed before and after implementation of the vaccine. Such information can provide real world effectiveness estimates on the reduction of morbidity and mortality and has been demonstrated correspondingly by the MenAfriVac® program after delivery of the monovalent serogroup A vaccine.

G. Conclusion

The objective of this review is to compare the schedules from clinical trials and long term follow-up studies to identify the most cost-effective and effective dosing strategies for serogroup C conjugate vaccines. Country-specific schedules must account for the regional age-specific distribution and incidence of disease. Routine immunization schedules should aim to achieve the highest levels of protection using the fewest doses possible. Our conclusions are based only on serogroup C antibody data and does not account for other meningococcal group A, W, or Y antibody responses when multivalent vaccines were administered. Available evidence suggests that 2 or fewer doses during infancy is highly effective and immunogenic, even beginning as early as 2 months of age. A separate comparison study of schedules from across Canada also found that 2 compared to 3 doses in infancy was equally efficacious and that this was only minimally superior to beginning vaccination for serogroup C meningococcal disease at 12 months of age [112]. Short term response to booster doses

was also higher in infants that receive fewer doses in infancy, even though their GMT was lower post primary series. In nearly all schedules TT carrier vaccines were more immunogenic than CRM carrier equivalents. This was less pronounced with 3 doses in infancy, and by 12 months of age antibody titers wane similarly regardless of the vaccine used. Single or booster doses given at 1-10 years of age maintain protective serum titers for 3 years in approximately 60-80% of children. Initial immunizations given after the age of 11 years is expected to provide immunity for the majority of children for a period of 5-7 years.

Several observational studies have concluded that Meningococcal serogroup C vaccines have played a significant role in decrease in transmission and incidence rates in the UK [113-115], Spain [116], Canada [117, 118], Greece [119], Brazil [120], and the Netherlands [121]. Conjugate vaccines were also shown to induce herd immunity by decreasing incidence in unvaccinated populations. Meningococcal disease is endemic worldwide and can cause serious complications or mortality even with treatment. Vaccinations provide the best opportunity for preventing and controlling infection. Meningococcal vaccines have been determined to be safe and effective when administered with all routine immunizations as early as two months of age for the prevention of meningococcal disease.

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Appendix A

Search Strategy:

Pubmed/MEDLINE Search-

(“Meningitis, Meningococcal"[Mesh] OR "Meningitis, Meningococcal/prevention and control"[Mesh] OR "Neisseria meningitidis, Serogroup C"[Mesh]) AND ("Vaccines"[Mesh] OR "Meningococcal Vaccines"[Mesh] OR "serogroup C meningococcal conjugate vaccine" [Supplementary Concept] OR “Conjugate Vaccines”[TIAB] OR “group C vaccine”[TIAB]) AND (("2004/01/01"[PDat] : "3000/12/31"[PDat]) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh]) NOT (“meningococcus B”[TIAB] OR “serogroup B”[TIAB] OR “Serogroup X”[TIAB])

CENTRAL –

meningococcal C conjugate vaccine" in Title, Abstract, Keywords or "meningococcal serogroup C conjugate vaccine" in Title, Abstract, Keywords or "meningococcal vaccine" in Title, Abstract, Keywords Publication Year from 2004 to 2014, in Cochrane Reviews (Reviews and Protocols), Other Reviews, Trials and Cochrane Groups (Word variations have been searched)

EMBASE – OvidSP –

1. Meningococcal Vaccines/
2. exp Clinical Trial/
3. xp Meningitis, Meningococcal/
4. Vaccines, Conjugate/
5. Random Allocation/
6. Neisseria meningitidis, Serogroup C/
7. conjugate vaccine$.mp.
8. randomized controlled trial/
9. exp Double-Blind Method/
10. exp Single-Blind Method/
11. exp Controlled Clinical Trial/
12. (random$ or blind$ or mask$ or singl$ or doubl$).m_titl.
13. exp Placebos/
14. 2 or 5 or 8 or 9 or 10 or 11 or 12 or 13
15. 3 or 6
16. 1 or 4 or 7
17. 15 and 16
18. 14 and 17

Global Index Medicus = (LILACS/AIM/IMEMR/WPRIM/IMSEAR)

"meningococcal vaccines [Subject] and “conjugate vaccines”[Subject]

Vita

Charles Brent Chesson was born in New Bern, North Carolina on August 31st, 1980. His parents, Thomas Bradford and Nan Gardner Chesson still reside in New Bern. Brent attended North Carolina State University where he received a bachelor of science in Microbiology, and the University of North Carolina at Charlotte where he received a bachelor of science in Chemistry with honors. Brent plans to graduate from the University of Texas Medical Branch with a Master's of Public Health in December 2015, and a Ph.D in Human Pathophysiology and Translational Medicine in May 2016.

Permanent address: 1610 Tryon Rd. New Bern, NC 28560

This thesis was typed by Charles Brent Chesson.