Vaccine 37 (2019) 3562–3567

Contents lists available at ScienceDirect

Vaccine

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

Effect on meningococcal serogroup W immunogenicity when Tdap was administered prior, concurrent or subsequent to the quadrivalent (ACWY) meningococcal CRM_{197}-conjugate vaccine in adult Hajj pilgrims: A randomised controlled trial

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

[a] The Discipline of Child and Adolescent Health, Children's Hospital Westmead Clinical School, Faculty of Medicine and Health, The University of Sydney, NSW, Australia
[b] Faculty of Medicine, University of Tripoli, Ain Zara, Tripoli, Libya
[c] National Centre for Immunisation Research and Surveillance (NCIRS), The Children's Hospital at Westmead, NSW, Australia
[d] Department of Family and Community Medicine, Faculty of Medicine in Rabigh, King Abdulaziz University, Jeddah, Saudi Arabia
[e] The Executive Administration of Research and Innovation, King Abdullah Medical City in Holy Capital (KAMC-HC), Makkah 24246, Saudi Arabia
[f] Saudi Food and Drug Authority, Riyadh 13312, Saudi Arabia
[g] Immunology Department, The Children's Hospital at Westmead, Westmead 2145, NSW, Australia
[h] Marie Bashir Institute for Infectious Diseases and Biosecurity, School of Biological Sciences and Sydney Medical School, University of Sydney, Sydney, NSW 2145, Australia
[i] Vaccine Evaluation Unit, Public Health England, Manchester Royal Infirmary, Manchester, UK
[j] WHO Collaborating Centre for Mass Gatherings and High Consequence/High Visibility Events, Flinders University, Adelaide 5001, Australia

ARTICLE INFO

Article history:
Received 18 March 2019
Received in revised form 7 May 2019
Accepted 8 May 2019
Available online 23 May 2019

Keywords:
Meningococcal conjugate vaccine
Carrier protein
Vaccine interaction
Diphtheria, tetanus, acellular pertussis vaccine
Serum bactericidal antibody

ABSTRACT

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

We studied the immune response to meningococcal serogroup W upon prior, concurrent and sequential administration of a quadrivalent meningococcal conjugate vaccine (MCV4) conjugated to CRM_{197} (coadministered with 13 valent pneumococcal vaccine conjugate CRM_{197} [PCV13]), and tetanus-diphtheria-acellular pertussis (Tdap) vaccine in Australian adults before attending the Hajj pilgrimage in 2014.

Participants were randomly assigned, by computer-generated numbers, to three study arms by 1:1:1 ratio. Group A received Tdap followed by MCV4-CRM_{197} (+PCV13) 3–4 weeks later. Group B received all three vaccines in a single visit. Group C received MCV4-CRM_{197} (+PCV13) followed by Tdap 3–4 weeks later. Blood samples obtained prior to and 3–4 weeks after immunisation with MCV4-CRM_{197} were tested for meningococcal serogroup W-specific serum bactericidal antibody responses using baby rabbit complement (rSBA).

One hundred and seven participants aged between 18 and 64 (median 40) years completed the study. No significant difference in meningococcal serogroup W rSBA geometric mean titre (GMT) was observed between the study arms post vaccination with MCV-CRM_{197} but Group A tended to have a slightly lower GMT (A = 404, B = 984 and C = 1235, $p = 0.15$). No statistical difference was noticed between the groups in proportions of subjects achieving a $\geq$4-fold rise in rSBA titres or achieving rSBA titre $\geq$8 post vaccination.

In conclusion, receipt of MCV4-CRM_{197} vaccine prior, concurrent or subsequent to Tdap has similar immunologic response, and hence concurrent administration is both immunogenic and practical. However, further investigation into whether carrier induced suppression is a public health issue is suggested.

Clinical trial registration: ANZCTR no. ACTRN12613000536763.

* Corresponding author at: National Centre for Immunisation Research and Surveillance (NCIRS), The Children's Hospital at Westmead, Cnr Hawkesbury Road and Hainsworth Street, Locked Bag 4001, Westmead, NSW 2145, Australia.
E-mail address: almamoon.badahdah@health.nsw.gov.au (A.-M. Badahdah).
[1] M. Tashani and A.M. Badahdah have made equal contributions.

https://doi.org/10.1016/j.vaccine.2019.05.025
0264-410X/

1. Introduction

Meningococcal disease and pneumococcal pneumonia are serious infections that affect the older population. Widespread childhood immunisation with conjugate vaccines in many developed countries has played a considerable role in terms of controlling disease and reducing mortality through direct and herd protection [1–4]. Conjugate vaccines surpass their polysaccharide counterparts as they are conjugated to carrier proteins responsible for converting the T-cell independent immunological response to T-cell dependent, thus provoking both B-cell and T-cell responses as well as establishing immunologic memory in all age groups [5]. The commonly used carrier proteins in licensed meningococcal polysaccharide-conjugate vaccines are: Diphtheria toxoid (DT), tetanus toxoid (TT) and non-toxic diphtheria toxin mutant protein (CRM_{197}) [6].

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

One occasion that may raise the concern of vaccine interference is the Hajj. The Hajj is a large annual mass gathering. Approximately 2.5 million Muslims from over 180 countries gather annually for a minimum 5-day period [20]. Intense congestion, shared accommodation and compromised hygiene amplify the risk of invasive meningococcal disease (IMD). Intercontinental Hajj related outbreaks of meningococcal serogroup A (MenA) occurred in 1987 [21], and of MenW in 2000–2001 [22]. Secondary cases of IMD have been reported in close contacts of returning pilgrims who may asymptomatically carry meningococci [23–25]. Therefore, the Kingdom of Saudi Arabia Ministry of Health applied certain measures to secure the health of pilgrims at the Hajj [26,27], notably the declaration in 2001 that quadrivalent meningococcal vaccine against serogroups A, C, W, and Y is mandatory for all Hajj or Umrah pilgrims. The use of a quadrivalent conjugate vaccine as a substitute for the polysaccharide vaccine when affordable/available is recommended [25,28]. The Saudi government also recommends other vaccines including DTP, seasonal influenza, polio, mumps, measles, and rubella (MMR), and yellow fever vaccines [29]. Some immunisation experts also recommend pneumococcal vaccine for those at increased risk of developing the disease [30].

Given that a considerable fraction of pilgrims may take several conjugate vaccines in a short period [31], there is potential for interferences between them and/or other vaccines containing antigens similar to carrier proteins, namely combined diphtheria-tetanus acellular pertussis vaccine (Tdap).

Pilgrims from developed countries are likely to receive the quadrivalent meningococcal conjugate vaccine (MCV4). Hajj pilgrimage provided a special opportunity to assess the interaction of MCV4 when administered before, with and after diphtheria-tetanus conditioning vaccines. To this end, we conducted two randomised controlled trials (RCT), in 2014 and in 2015, among adult Australians who were preparing to be pilgrims, to evaluate the immunogenicity of MCV4 coadministered with 13-valent pneumococcal CRM_{197} conjugate vaccine (PCV13-CRM_{197}) when administered before, with and after Tdap. Both trials had very similar design, the only difference being the type of carrier protein conjugated to the MCV4 used: MCV4 conjugated to CRM_{197} (MCV4-CRM_{197}) in 2014, and MCV4 conjugated to TT (MCV4-TT) in 2015. Results for antibody against pneumococcal disease have been published previously [32–34]. However, the meningococcal responses was only reported for the 2015 trial [35]; since MenW was the only serogroup to have a statistically significant reduction in serum bactericidal antibody (rSBA) response 3–4 weeks following MCV4-TT injection (when Tdap was given first), we conducted this analysis to examine and compare the effect of sequential and concurrent administration of Tdap and MCV4-CRM_{197} on antibody against the MenW antigen among participants in the 2014 trial.

2. Material and methods

2.1. Study design

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

2.2. Objectives

The primary objective was to establish whether prior, concurrent or subsequent use of Tdap, influences antibody responses to MCV4 and PCV13-CRM_{197}. In this analysis, only the response to MenW antigen (contained in MCV4-CRM_{197}) was examined as it was the only serogroup to demonstrate statistically significant difference in the previous study (using MCV4-TT) [35]. Diphtheria, tetanus and pneumococcal, antibody results as well as assessment of safety and reactogenicity have been reported previously [32].

2.3. Participants

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

2.4. Random assignment

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

Group A: Vaccinated with Tdap (Boostrix™, GlaxoSmithKline) at first visit (left deltoid) then, 3–4 weeks later, followed by coadministration of MCV4-CRM_{197} (Menveo™, GlaxoSmithKline) and PCV13-CRM_{197} (Prevnar™, Pfizer) in the left deltoid and right deltoid muscles, respectively.
Group B: Concurrently vaccinated with Tdap in the left deltoid muscle and MCV4-CRM_{197} (lower right deltoid muscle) plus PCV13-CRM_{197} (upper right deltoid muscle).

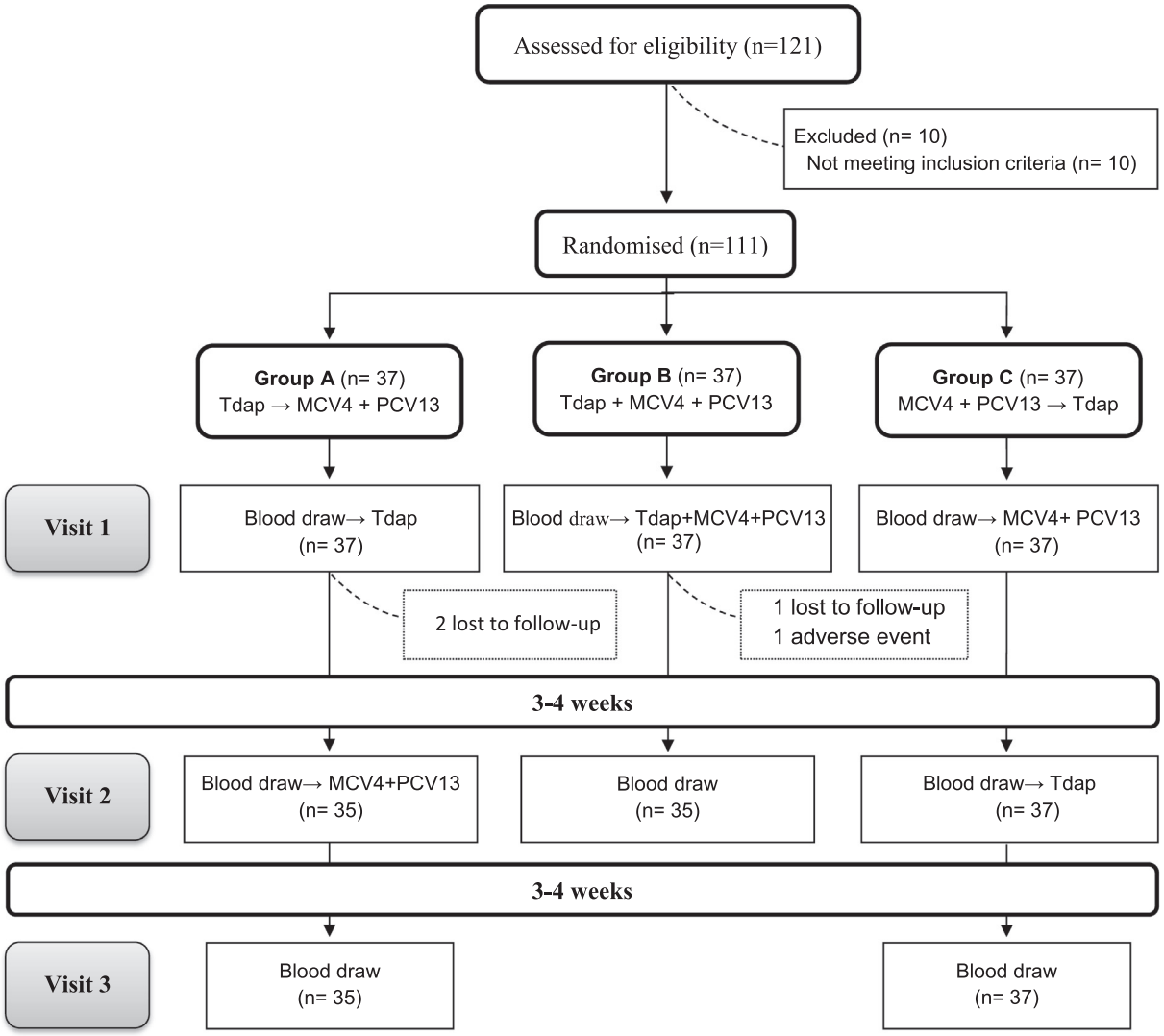

Fig. 1. Subject disposition flowchart. Group A: initially Tdap then MCV4 plus PCV13; Group B: administered all vaccines concurrently; Group C: MCV4 plus PCV13 then Tdap. MCV4: quadrivalent meningococcal CRM_{197} conjugate vaccine; PCV13: 13 valent pneumococcal CRM_{197}-conjugate vaccine; Tdap: combined tetanus, reduced diphtheria and acellular pertussis vaccine.

Group C: Initially coadministered PCV13-CRM_{197} (in the right deltoid muscle) and MCV4-CRM_{197} (in the left deltoid muscle) followed by Tdap injection (in the left deltoid muscle) 3–4 weeks later.

2.5. Blood sample collection

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

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

2.6. Statistical analysis

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

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

2.7. Ethics approval and trial registration

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

3. Results

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

rSBA titre results for *N. meningitidis* serogroup W are summarised in Table 1. There was no significant difference in MenW rSBA GMTs between the three study arms 3–4 weeks following the receipt of MCV-CRM_{197} dose but giving Tdap after MCV4-CRM_{197} was suggestive of a slightly better response (A = 404, B = 984 and C = 1235, $p = 0.15$). Comparing the proportions of participants who achieved at least 4-fold increases in rSBA titre post-vaccination compared to prevaccination titre between the groups suggests no interference with MenW antibody response ($p = 0.67$) when Tdap was given 3–4 weeks before, after, or with MCV4-CRM_{197} + PCV13-CRM_{197}: 82.9% of Group A subjects who received Tdap 3–4 weeks prior to MCV4-CRM_{197} + PCV13-CRM_{197} achieved rSBA titre rise of ≥4-fold in response to MenW compared to 88.6% of Group B (coadministered all vaccines at the same time) and 81.1% of Group C subjects (initially received MCV CRM_{197}/PCV13-CRM_{197} followed by Tdap 3–4 weeks later).

The proportion of subjects with rSBA titre ≥8 (seropositive) for MenW after receiving MCV4-CRM_{197} + PCV13-CRM_{197} was also similar ($p = 0.33$) across the groups: Group A (82.9%), Group B (94.3%) and Group C (86.5%).

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

4. Discussion

The study aimed to evaluate the immunogenicity of the MenW polysaccharide component of MCV4 conjugated to CRM_{197} (coadministered with PCV-CRM_{197}), when administered before, with and after Tdap among adults. All three study arms had a similar immunological response in term of GMTs, seroresponse and seroprotection, with no statistical evidence of interference with or enhancement of the immunogenicity of the MenW polysaccharide but numbers were quite small. On the other hand, achievement of ≥4-fold rise in rSBA titres (seroresponse) to MenW was significantly lower, in the group exposed to prior Tdap 3–4 weeks, when a TT-conjugated MCV4 was used during the 2015 trial [35].

Results from other studies suggested that prior or concurrent exposure to diphtheria-tetanus containing vaccines does not affect the immune response to MCV4, which is consistent with our finding [14,38–40]. For instance, one trial showed that administration of MCV4-CRM_{197} prior to or simultaneously with Tdap did not alter its immunogenicity [38]. Another trial, in a study involving preschool and school age children, showed no effect on the immunogenicity of MCV4-CRM_{197} neither upon prior nor concurrent receiving of diphtheria-tetanus booster [14]. This non-inferiority was also observed when concurrent versus consecutive administration of MCV4-DT with Tdap was investigated in adolescents [39]. Additionally, a review of MCV4-TT showed also an intact immunogenicity upon concurrent administration in infants and toddlers with other vaccines including Tdap or 10-valent pneumococcal *Haemophilus influenzae* protein D conjugate vaccine (PCV10) [40].

On the other hand, a study involving adolescents observed a significantly lower proportion of seroresponders to MenW when Tdap was administered sometime before MCV4-CRM_{197} [38], which was consistent with our finding in the 2015 trial using MCV4-TT [35]. Furthermore studies revealed a suppression outcome in the Burrage trial where previous receipt of a tetanus containing vaccine reduced the immune response to meningococcal C vaccine conjugated to TT (MenC-TT) polysaccharide, although a protective threshold was achieved [14]. Similarly, another RCT among teenagers reported that the immune response to MenC, Y and W polysaccharide was lower with sequential administration, namely when diphtheria toxoid-adsorbed vaccine (Td) was given a month before MCV4-DT [41]. Another recent trial reported that the proportions of subjects with an adequate immunological response against MenA, C and W was lower when MCV4-TT vaccine was given to a toddlers aged 12–23 months after a previous DTP shot [42]. A trial among Korean military recruits in 2013 has shown that just a three days gap between administration of tetanus-diphtheria toxoids and MCV4-CRM_{197} resulted in a significant suppression [43].

Conversely, in other trials, both concurrent [44] or prior exposure [45,46] to DTP or its components improved the immune response to both monovalent C conjugate vaccine and MCV4 among humans and in animal models. For instance, adult mice with previous exposure to TT had shown an enhanced immunogenicity to MenC-TT [46].

This degree of inconsistency was much less seen when analysing immune responses to PCV13-CRM_{197} in both our studies in

Table 1
Meningococcal serogroups W rSBA GMTs post vaccination, and proportions of seroresponders (≥4-fold rise in rSBA titre between sample collected prior to and 3 to 4 weeks post vaccination with MCV4 + PCV13) and seropositive subjects (rSBA ≥8, 3 to 4 weeks following receipt of MCV4 + PCV13); for MCV4 (coadministered with PCV13) when MCV4 + PCV13 injected before, concurrently or after Tdap.

	Group A (n = 35)	Group B (n = 35)	Group C (n = 37)	*p*-value
rSBA GMT (95% CI)	404 (172–949)	984 (419–2313)	1235 (538–2835)	0.15[a]
Seroresponse, n (%)	29 (82.9%)	31 (88.6%)	30 (81.1%)	0.67[b]
Seropositive, n (%)	29 (82.9%)	33 (94.3%)	32 (86.5%)	0.33[b]

Group A: Tdap before MCV4-CRM_{197} and PCV13-CRM_{197}; Group B: Tdap with MCV4-CRM_{197} and PCV13-CRM_{197}; Group C: MCV4-CRM_{197} and PCV13-CRM_{197} before Tdap. GMT: Geometric mean titre; MCV4: quadrivalent meningococcal-CRM_{197} conjugate vaccine; PCV13: 13-valent pneumococcal-CRM_{197} conjugate vaccine; Tdap: combined tetanus, reduced diphtheria and acellular pertussis vaccine.

[a] : ANOVA test.

[b] : Chi-square test.

which prior receipt of Tdap in adults had significantly reduced the antibody response to six [32] and to seven [33] of the 13 antigens present in PCV13-CRM_{197}. This consistent finding may be explained by the fact that the pneumococcal vaccine used (PCV13-CRM_{197}) was not changed in both trials. Alternatively, this may demonstrate that polysaccharide components (pneumococcal vs. meningococcal) of the conjugate vaccine themselves could act differently even when both conjugated to the same carrier proteins.

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

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

The small sample size is a key limitation of this study and an increased number of participants could offer a better demonstration of the effect. The long duration between sampling and testing is yet another limitation. Coadministration of another conjugate vaccine (PCV13-CRM_{197}) has limited the ability to relate the observed effect solely to Tdap, and further head to head analysis is suggested.

Multiple vaccine administration on a single occasion reduces clinic visits, and thus decreases cost and may enhance compliance. Nevertheless, some practitioners favour separate administration to avoid possible interactions or exaggerated adverse events. Travellers such as Hajj pilgrims are usually required to receive more than one vaccine in a short period of time. There is no apparent evidence against giving MCV4-CRM_{197} or MCV4-TT with Tdap in a single visit to achieve better compliance. However, if separation is required (e.g. when adverse events are suspected) this study showed no difference whether the conjugated vaccines (MCV4/PCV13) were given before or after the antigen containing vaccine (Tdap).

Recent recommendations prefer the conjugate vaccine for pilgrims over its plain polysaccharide rival. Over the past two years, the MCV4 vaccine has completely replaced the polysaccharide in Australia. Being not funded for pilgrims by governments in most developed countries cost as a concern will rise, as MCV4 is significantly more expensive than plain polysaccharide. However, knowing that both (TT and CRM_{197}-conjugated vaccine) can be safely administered with PCV-CRM_{197} and Tdap will provide more convenient options to the pilgrims.

This paper concludes reporting on two RCTs with identical design and similar vaccines, but different carrier proteins, conducted in 2014 and 2015. Results of this analysis are consistent with those previously published. Prior exposure to Tdap could suppress the immunological response to PCV13-CRM_{197} and to MCV4-TT. Our current study with MCV4-CRM_{197} showed differences in the same direction but not significant. This may be due to lack of power.

5. Conclusion

Based on this study we continue to support concurrent administration of MCV4-CRM_{197} and Tdap. However, we suggest further investigation into whether carrier induced suppression is a public health issue.

Declaration of Competing Interest

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

Acknowledgment

Richard Pryce-Williams, PHE Manchester, UK for laboratory work. Mohamed Tashani would like to acknowledge the Islamic Development Bank (IsDB) for providing financial support.

References

[1] Avci FY. Novel strategies for development of next-generation glycoconjugate vaccines. Curr Top Med Chem 2013;13:2535–40.
[2] Watt JP, Wolfson LJ, O'Brien KL, Henkle E, Deloria-Knoll M, McCall N, et al. Burden of disease caused by Haemophilus influenzae type b in children younger than 5 years: global estimates. Lancet 2009;374:903–11.
[3] O'Brien KL, Wolfson LJ, Watt JP, Henkle E, Deloria-Knoll M, McCall N, et al. Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. Lancet 2009;374:893–902.
[4] Trotter CL, Andrews NJ, Kaczmarski EB, Miller E, Ramsay ME. Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction. Lancet 2004;364:365–7.
[5] Harrison LH. Prospects for vaccine prevention of meningococcal infection. Clin Microbiol Rev 2006;19:142–64.
[6] Vipond C, Care R, Feavers IM. History of meningococcal vaccines and their serological correlates of protection. Vaccine 2012;30(Suppl 2):B10–7.
[7] Broder KR, Cortese MM, Iskander JK, Kretsinger K, Slade BA, Brown KH, et al. Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2006;55:1–34.
[8] Centers for Disease Control and Prevention. Outbreaks of group B meningococcal disease–Florida, 1995 and 1997. MMWR Morb Mortal Wkly Rep. 1998;47:833–7.
[9] Wong CA, Taylor JA, Wright JA, Opel DJ, Katzenellenbogen RA. Missed opportunities for adolescent vaccination, 2006–2011. J Adolesc Health 2013;53:492–7.
[10] Dagan R, Poolman JT, Zepp F. Combination vaccines containing DTPa-Hib: impact of IPV and coadministration of CRM197 conjugates. Expert Rev Vaccines 2008;7:97–115.
[11] Pobre K, Tashani M, Ridda I, Rashid H, Wong M, Booy R. Carrier priming or suppression: understanding carrier priming enhancement of anti-polysaccharide antibody response to conjugate vaccines. Vaccine 2014;32:1423–30.
[12] Pollabauer EM, Petermann R, Ehrlich HJ. The influence of carrier protein on the immunogenicity of simultaneously administered conjugate vaccines in infants. Vaccine 2009;27:1674–9.
[13] Barington T, Skettrup M, Juul L, Heilmann C. Non-epitope-specific suppression of the antibody response to Haemophilus influenzae type b conjugate vaccines by preimmunization with vaccine components. Infect Immun 1993;61:432–8.

[14] Burrage M, Robinson A, Borrow R, Andrews N, Southern J, Findlow J, et al. Effect of vaccination with carrier protein on response to meningococcal C conjugate vaccines and value of different immunoassays as predictors of protection. Infect Immun 2002;70:4946–54.
[15] Mulholland K, Suara RO, Siber G, Roberton D, Jaffar S, N'Jie J, et al. Maternal immunization with Haemophilus influenzae type b polysaccharide-tetanus protein conjugate vaccine in The Gambia. JAMA 1996;275:1182–8.
[16] Lucero MG, Puumalainen T, Ugpo JM, Williams G, Kayhty H, Nohynek H. Similar antibody concentrations in Filipino infants at age 9 months, after 1 or 3 doses of an adjuvanted, 11-valent pneumococcal diphtheria/tetanus-conjugated vaccine: a randomized controlled trial. J Infect Dis 2004;189:2077–84.
[17] Spijkerman J, Veenhoven RH, Wijmenga-Monsuur AJ, Elberse KE, van Gageldonk PG, Knol MJ, et al. Immunogenicity of 13-valent pneumococcal conjugate vaccine administered according to 4 different primary immunization schedules in infants: a randomized clinical trial. JAMA 2013;310:930–7.
[18] Tashani M, Jayasinghe S, Harboe ZB, Rashid H, Booy R. Potential carrier priming effect in Australian infants after 7-valent pneumococcal conjugate vaccine introduction. World J Clin Pediatr 2016;5:311–8.
[19] Shelly MA, Pichichero ME, Treanor JJ. Low baseline antibody level to diphtheria is associated with poor response to conjugated pneumococcal vaccine in adults. Scand J Infect Dis 2001;33:542–4.
[20] Memish ZA, Stephens GM, Steffen R, Ahmed QA. Emergence of medicine for mass gatherings: lessons from the Hajj. Lancet Infect Dis 2012;12:56–65.
[21] Wilder S. Meningococcal vaccine in travelers. Curr Opin Infect Dis 2007;20:454–60.
[22] Ahmed QA, Arabi YM, Memish ZA. Health risks at the Hajj. Lancet 2006;367:1008–15.
[23] Aguilera JF, Perrocheau A, Meffre C, Hahne S, Group WW. Outbreak of serogroup W135 meningococcal disease after the Hajj pilgrimage, Europe, 2000. Emerg Infect Dis 2002;8:761–7.
[24] Hahne SJ, Gray SJ, Jean F, Aguilera, Crowcroft NS, Nichols T, et al. W135 meningococcal disease in England and Wales associated with Hajj 2000 and 359 2001. Lancet 2002:582–3.
[25] Ceyhan M, Celik M, Demir ET, Gurbuz V, Aycan AE, Unal S. Acquisition of meningococcal serogroup W-135 carriage in Turkish Hajj pilgrims who had received the quadrivalent meningococcal polysaccharide vaccine. Clin Vaccine Immunol 2013;20:66–8.
[26] Yezli S, Elganainy A, Awam A. Strengthening health security at the Hajj mass gatherings: a Harmonised Hajj Health Information System. J Travel Med 2018;25.
[27] Alotaibi BM, Yezli S, Bin Saeed AA, Turkestani A, Alawam AH, Bieh KL. Strengthening health security at the Hajj mass gatherings: characteristics of the infectious diseases surveillance systems operational during the 2015 Hajj. J Travel Med 2017;24.
[28] Alqahtani AS, Heywood AE, Rashid H. Preparing Australian pilgrims for the Hajj 2018. J Travel Med 2018;25.
[29] Health conditions for travellers to Saudi Arabia for the pilgrimage to Mecca (Hajj), 2016. Wkly Epidemiol Rec. 2016;91:331–5.
[30] Rashid H, Abdul Muttalif AR, Mohamed Dahlan ZB, Djauzi S, Iqbal Z, Karim HM, et al. The potential for pneumococcal vaccination in Hajj pilgrims: expert opinion. Travel Med Infect Dis 2013;11:288–94.
[31] Alqahtani AS, Wiley KE, Tashani M, Willaby HW, Heywood AE, BinDhim NF, et al. Exploring barriers to and facilitators of preventive measures against infectious diseases among Australian Hajj pilgrims: cross-sectional studies before and after Hajj. Int J Infect Dis 2016;47:53–9.
[32] Tashani M, Alfelali M, Barasheed O, Alqahtani AS, Heron L, Wong M, et al. Effect of Tdap when administered before, with or after the 13-valent pneumococcal conjugate vaccine (coadministered with the quadrivalent meningococcal conjugate vaccine) in adults: a randomised controlled trial. Vaccine 2016;34:5929–37.
[33] Tashani M, Heron L, Wong M, Rashid H, Booy R. Tetanus-diphtheria-pertussis vaccine may suppress the immune response to subsequent immunization with pneumococcal CRM197-conjugate vaccine (coadministered with quadrivalent meningococcal TT-conjugate vaccine): a randomized, controlled trial small star, filled. J Travel Med 2017;24.
[34] Badahdah AM, Tashani M, Khatami A, Booy R, Rashid H. Interaction of meningococcal conjugate vaccines with other conjugate or diphtheria-tetanus containing vaccines. J Travel Med 2018;25.
[35] Tashani M, Alfelali M, Barasheed O, Alqahtani AS, Heron L, Wong M, et al. Effect of Tdap upon antibody response to meningococcal polysaccharide when administered before, with or after the quadrivalent meningococcal TT-conjugate vaccine (coadministered with the 13-valent pneumococcal CRM197-conjugate vaccine) in adult Hajj pilgrims: a randomised controlled trial. Vaccine 2018;36:4375–82.
[36] Australian Technical Advisory Group on Immunisation (ATAGI). The Australian immunisation handbook 10th ed (2015 update). Canberra: Australian Government Department of Health; 2015.
[37] Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I. The role of humoral antibodies. J Exp Med 1969;129:1307–26.
[38] Arguedas A, Soley C, Loaiza C, Rincon G, Guevara S, Perez A, et al. Safety and immunogenicity of one dose of MenACWY-CRM, an investigational quadrivalent meningococcal glycoconjugate vaccine, when administered to adolescents concomitantly or sequentially with Tdap and HPV vaccines. Vaccine 2010;28:3171–9.
[39] Weston WM, Friedland LR, Wu X, Howe B. Immunogenicity and reactogenicity of co-administered tetanus-diphtheria-acellular pertussis (Tdap) and tetravalent meningococcal conjugate (MCV4) vaccines compared to their separate administration. Vaccine 2011;29:1017–22.
[40] Hedari CP, Khinkarly RW, Dbaibo GS. Meningococcal serogroups A, C, W-135, and Y tetanus toxoid conjugate vaccine: a new conjugate vaccine against invasive meningococcal disease. Infect Drug Resist 2014;7:85–99.
[41] Sanofi Pasteur Inc. 2018. Menactra® full prescribing information [Online]. Available from<https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm131170.pdf>. [accessed in March 2019].
[42] Knuf M, Kowalzik F, Kieninger D. Comparative effects of carrier proteins on vaccine-induced immune response. Vaccine 2011;29:4881–90.
[43] Kim HW, Park IH, You S, Yu HT, Oh IS, Sung PS, et al. Immunogenicity of MenACWY-CRM in korean military recruits: influence of tetanus-diphtheria toxoid vaccination on the vaccine response to MenACWY-CRM. Yonsei Med J 2016;57:1511–6.
[44] Broderick MP, Romero-Steiner S, Rajam G, Johnson SE, Milton A, Kim E, et al. Immune responses in U.S. military personnel who received meningococcal conjugate vaccine (MenACWY) concomitantly with other vaccines were higher than in personnel who received MenACWY alone. Clin Vaccine Immunol 2016;23:672–80.
[45] Tejedor JC, Moro M, Merino JM, Gomez-Campdera JA, Garcia-del-Rio M, Jurado A, et al. Immunogenicity and reactogenicity of a booster dose of a novel combined Haemophilus influenzae type b-Neisseria meningitidis serogroup C-tetanus toxoid conjugate vaccine given to toddlers of 13–14 months of age with antibody persistence up to 31 months of age. Pediatr Infect Dis J 2008;27:579–88.
[46] Peeters CC, Tenbergen-Meekes AM, Poolman JT, Beurret M, Zegers BJ, Rijkers GT. Effect of carrier priming on immunogenicity of saccharide-protein conjugate vaccines. Infect Immun 1991;59:3504–10.
[47] Delves PJ, Martin SJ, Burton DR, Roitt IM. Essential immunology. Wiley; 2017.
[48] Dagan R, Poolman J, Siegrist CA. Glycoconjugate vaccines and immune interference: a review. Vaccine 2010;28:5513–23.
[49] Alberer M, Burchard G, Jelinek T, Reisinger EC, Meyer S, Dagnew AF, et al. Immunogenicity and safety of concomitant administration of a combined hepatitis A/B vaccine and a quadrivalent meningococcal conjugate vaccine in healthy adults. J Travel Med 2014;22:105–14.
[50] Alberer M, Burchard G, Jelinek T, Reisinger E, Beran J, Hlavata LC, et al. Safety and immunogenicity of typhoid fever and yellow fever vaccines when administered concomitantly with quadrivalent meningococcal ACWY glycoconjugate vaccine in healthy adults. J Travel Med 2015;22:48–56.