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Persistence of bactericidal antibodies following booster vaccination with 4CMenB at 12, 18 or 24 months and immunogenicity of a fifth dose administered at 4 years of age—a phase 3 extension to a randomised controlled trial

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Abstract

Background: 4CMenB is immunogenic in infants and toddlers. We assessed persistence of human complement serum bactericidal activity (hSBA) following a fourth dose administered at 12, 18 or 24 months and characterised the antibody response to a fifth dose administered at 4 years of age.

Methods: A phase 3, open label, multi-centre extension to a randomised controlled trial conducted in four countries (number of centres): Czech Republic (nineteen), Italy (four), Spain (four) and the United Kingdom (four). Four-year-old children who were either 4CMenB-naïve or had previously received a variety of 3-dose infant priming schedules and a booster vaccine as toddlers (follow-on group) were recruited. Venous blood samples were obtained to determine hSBA against four reference strains; acting as targets to assess immunity to each of the vaccine antigens, NadA (5/99), fHbp (H44/76), PorA (NZ98/254), and NHBA (M10713) at baseline (prior to vaccination, all participants) and one month following a dose of 4CMenB for all vaccine-naïve and follow-on participants primed with the 2, 3, 4 schedule, and a third of follow-on participants primed with a 2, 4, 6 month schedule.

Results: At baseline (prior to vaccination), the proportion of participants (n = 468) with hSBA titers ≥ 5 was similar across all followon groups: 89–100% against 5/99; 12–35% for H44/76; 8–12% for NZ98/254 and 53–80% for M10713 compared with 5%, 0%, 0%; and 60% respectively, for the vaccine-naïve controls (n = 206). Following a dose of 4CMenB at 4 years of age, this increased to 100% (5/99), 97–100% (H44/76), 80–95% (NZ98/254) and 84–100% (M10713) (n = 210), compared with 89%, 70%, 24%, and 76% respectively for vaccine-naïve controls (n = 192).

Conclusion: Waning of protective antibodies occurred 12–36 months after toddler booster regardless of age at boost. This was least marked against target strains 5/99 and M10713. A robust memory response occurred after a booster dose given at 4 years of age.

1. Introduction

The licensed four-component capsular group B meningococcal vaccine (4CMenB) was introduced into the UK routine infant immunisation programme in September 2015 [1]. Demonstration
of immunogenicity of this vaccine in a range of infant and toddler immunisation schedules is important to establish its potential in the varied international vaccine programmes. Whilst antibody responses and persistence following different vaccination schedules in infancy [2] and toddler years [3–5] have been described, data on the impact of the previously received vaccination schedule on long term bactericidal antibody persistence and by extrapolation, protection against disease, are few.

In this study we assessed persistence of bactericidal antibodies to 4 years following a fourth dose of 4CMenB given at either 12, 18 or 24 months of age to participants who had received different 4CMenB priming schedules in infancy. In addition, we investigated the antibody response and reactogenicity following a fifth dose of 4CMenB given at 4 years of age.

2. Methods

2.1. Study design

A Phase 3, open label, multi-centre extension to a randomised controlled trial conducted (November 2012 to October 2013) in Czech Republic, Italy, Spain, and the United Kingdom (nineteen, four, four, four centres respectively). Recruitment in the UK was via mail out of information letters through the National Health Service child health computer databases. In other centres, this was through paediatric hospitals or private practices. This study was conducted in accordance with the provisions of the Declaration of Helsinki (1996) and the International Conference on Harmonization Guidelines for Good Clinical Practice and appropriate regulatory approval was obtained from relevant authorities in each participating country prior to recruitment.

2.2. Study objectives

The primary objective was to explore antibody persistence to 4 years of age after a fourth dose of 4CMenB administered in toddler years. Secondary objectives included characterisation of antibody response to, and tolerability of a fifth dose of 4CMenB.

2.3. Participant selection and randomisation

In the original infant study [2], participants were randomised (2:2:1:1) to receive 4CMenB either at (a) 2, 4, 6 months of age with routine immunisation (246Con), (b) 2, 4, 6 months of age, with routine vaccines at 3, 5, 7 months of age (246Int), or (c) 2, 3, 4 months concomitant with routine vaccines (234Con), while a fourth group of infants received routine vaccines alone (Control). In the first extension study [5], previously immunised participants were randomised (1:1:1) to receive a fourth dose at 12, 18 or 24 months of age. In addition, follow-on participants from the Control group of the original infant study as well two new Control groups of 4CMenB-naïve participants received two catch-up doses at 12 and 14, 18 and 20, and 24 and 26 months.

Healthy 4-year-old children who completed the vaccination course in the first extension study were invited to participate in this study. Inclusion and exclusion criteria are shown in Table 1 Supplementary file.

Groups 246Con and 246Int participants were randomised in a 2:1 ratio to a non-vaccination subset (subset#1) and a vaccination subset (subset#2) using a randomisation list produced by a validated system used by the Novartis Vaccine Diagnostics. The randomisation sequence within each group was executed with a permuted block size of 3. Allocation until the point of enrolment was masked from parents of participants through the use of sealed opaque envelopes. Group allocation was not masked from study staff and parents of participants after enrolment, but the label code ensured binding of the laboratory personnel.

Participants assigned to subset #1 were evaluated for antibody persistence alone. Participants assigned to subset #2 and all participants from Group 234Con received a fifth dose of 4CMenB and were evaluated for both persistence and antibody response. An additional group of healthy 4CMenB-naïve 4-year-old children were recruited to act as a comparison group for antibody persistence and response to single dose of 4CMenB. All ‘control’ follow-on participants from the two previous studies received a third dose of 4CMenB and were also evaluated for both persistence and antibody response. Data from this cohort are presented elsewhere [6].

2.4. Study vaccine

4CMenB consisted of 50 μg each of Neisserial adhesin A (NadA), and fusion proteins containing Neisseria heparin binding antigen (NHBA) and Factor H binding protein (fHbp), 25 μg detoxified OMV from N. meningitidis strain NZ298/254, 1.5 mg aluminium hydroxide and 10 mM histidine in 0.5 ml water for injection (Lot number 112801). This was administered by intramuscular injection into the deltoid muscle of the non-dominant arm, using a 23G needle.

2.5. Immunogenicity evaluation

Venous blood samples were collected at baseline (prior to vaccination) and 30 (–4/+10) days after each 4CMenB dose to determine hSBA against three chosen target strains selected to broadly determine responses to the individual target strains: 5/99 (NadA), 44/76-SL (fHbp), and NZ98/254 (OMV).

As previously described [7], an additional strain M10713 was included post hoc and assessed to determine SBA response against NHBA. hSBA was expressed as interpolated titers according to reciprocal serum dilutions yielding 50% or greater killing of the target strain after 60 min of incubation compared with growth at time 0. An interpolated titre ≥ 5 represented 95% confidence that participants achieving this titre had a protective hSBA (≥ 1: 4) [8]. The Novartis Vaccines Clinical Sciences Laboratory, Marburg, Germany performed the serological analysis.

2.6. Reactogenicity evaluation

All participants were observed for approximately 30 min after each vaccination for any reactions. Parents recorded and graded both local injection site and systemic reactions (Table 2, Supplementary File) for seven days following vaccination. Safety follow-up was completed 6 months after the last dose of 4CMenB. All serious adverse events (SAEs) reported during the study were recorded; the relationship between adverse events and the study vaccine was determined by a study investigator.

2.7. Statistical analysis

The pre-specified analysis population for immunogenicity was the Full analysis set (FAS) population, consisting all participants who provided at least one evaluable serum sample either at baseline (Persistency immunogenicity population) or after receipt of 4CMenB (Immunogenicity population). Antibody persistence was determined by calculating, for each of four indicator strains, the percentage of participants with hSBA titres ≥ 5 at baseline and associated two-sided 95% Clopper-Pearson confidence intervals (CIs). In addition, hSBA titers were log transformed and their geometric mean titers (GMTs), and associated 2-sided 95% CI were computed per study group and per strain using two-way analysis of variance with factors for vaccine group and country. Safety...
was assessed in terms of the number of participants per study group reporting local and systemic adverse events (AEs) and/or SAEs after vaccination. All participants who received at least one immunisation and provided some safety data were included in safety analyses. Safety results are reported descriptively.

The sample size for the follow-on groups was determined using the number of participants in the first extension study who were eligible to participate in this study. For the 4CMenB-naive group, 190 participants were needed to detect an underlying percentage immune response rate of 80% for reference strains 44/76-SL, 5/99, NZ98/254 with 80% power, assuming a 15% dropout rate. Statistical analysis was performed using SAS version 9.1 and independent validation of the analysis using SAS version 9.3 (SAS Institute, Cary, NC).

3. Results

Participant disposition is shown in Fig. 1. A total of 682 participants [non-vaccination group = 242; booster vaccination group = 231; vaccine-naive controls = 209] were enrolled from the four countries [Italy: 140 (20.5%), Czech Republic: 187 (27.4%), Spain: 87 (12.8%), United Kingdom: 268 (39.3%)]. There were 355 (52%) male and 327 (48%) female participants. The median age at the time of enrollment was 51 months (range 48–59 months). The most common self-defined ethnicity was white (97%). Baseline demographic data are summarised in Table 1.

3.1. Antibody persistence to 4 years of age

The proportions of participants with hSBA ≥ 5 for each target strain are shown in Table 2 and Fig. 1 Supplementary File. These were similar across all follow-on groups, being 100% for 5/99; 97–100% for 44/76-SL; 80–95% for NZ98/254 and 84–100% for M10713 and were generally lower in the naïve control group (88%, 70%, 24%, and 76% respectively). Against three of the four target strains (5/99, 44/76-SL, NZ98/254), hSBA GMTs were higher in the follow-on groups than the vaccine-naive controls (Table 3, Fig. 2) but were similar for the follow-on and vaccine-naive controls for NHBA.

The proportions of participants with a 4-fold increase in hSBA titres one month following vaccination in the follow-on groups ranged from 85–100% (for 5/99); 92–100% (44/76-SL); 61–88% (NZ98/254); 31–49% (M10713) and were 90%; 73%; 27% and 24% respectively for the vaccine-naive group (Table 2).

3.2. Antibody response to vaccination at 4 years of age

The proportions of participants reporting solicited AEs are shown in Table 2 Supplementary File. Reactogenicity was similar across all follow-on groups. Most solicited reactions were experienced within 6–24 h, a declining trend observed for all reactions in the seven days following vaccination (Fig. 2 Supplementary File). The most reported solicited local adverse event was transient injection site pain, experienced by (follow on vs. vaccine-naïve) 84–100% of participants (severe in 11–32%) and 91% (severe in 13%) respectively. Most pain was experienced within the first two days following vaccination, with 4–11% of follow-on, and 1–6% of vaccine-naive participants still experiencing pain seven days post vaccination.

3.3. Reactogenicity to vaccination at 4 years of age

The proportions of participants reporting solicited AEs are shown in Table 2 Supplementary File. Reactogenicity was similar across all follow-on groups. Most solicited reactions were experienced within 6–24 h, a declining trend observed for all reactions in the seven days following vaccination (Fig. 2 Supplementary File). The most reported solicited local adverse event was transient injection site pain, experienced by (follow on vs. vaccine-naïve) 84–100% of participants (severe in 11–32%) and 91% (severe in 13%) respectively. Most pain was experienced within the first two days following vaccination, with 4–11% of follow-on, and 1–6% of vaccine-naive participants still experiencing pain seven days post vaccination.

Fig. 1. Study flow diagram.
The most reported solicited systemic reaction was irritability, reported in 47–74% of follow-on participants (severe in 2–12%) compared with 33% (severe in 4%) for the vaccine-naive group. Fever rates in the follow-on group participants were 4–21% (severe (≥39 °C) in 2–6%; treated in 6–25%; medically attended in 2–7%), compared with 10% (severe in 1%; treated in 11%; medically attended in 1%) for the vaccine-naive group. Most fever occurred within 6 h post vaccination and resolved by day 3–4 post vaccination for majority of participants with the exception of those in study groups 246Con24 and 234Int12 and the vaccine-naive group of which 7–8%; 2% and 1–3% respectively still reported fever between day 4 and 6 post vaccination. Fever completely resolved by day 7 post vaccination (follow-on participants) but persisted in 2% of the vaccine-naive participants at this time.

SAEs observed within a month of the first vaccine were croup and trauma. Both were judged not related to the study vaccine.

### 4. Discussion

This is the first study to report data on persistence of immune responses to 4-years of age and in particular, the pattern of decline of antibodies for the different reference strains following infant priming and different 4CMenB boosting schedules in the second year of life. The data show that the pattern of the decline in bacterial antibodies 24–36 months after boosting was similar for the different follow-on groups, suggesting that the age at priming or boosting does not impact on antibody persistence following toddler vaccination. Of note, the magnitude of this decline varied by strain. In the absence of data reporting on the role of relatively persistent bacterial antibodies in long-term protection against strains bearing the relevant antigens, it is unclear whether this finding is of clinical relevance or only reflects different susceptibility of the target strains strain to killing in the SBA assay. Despite the decline, bacterial antibody titres at baseline in this study (i.e. point of enrolment and prior to vaccination) were higher in the follow-on groups than in the 4CMenB naïve group for three of the target strains tested (5/99, 44/76-SL, NZ98/254). Even though the target strains selected are thought to be indicative of the immune response to NadA, fHBP and PorA, the relation between test strain and vaccine antigen is likely to be more nuanced due to additional antigen components in the OMV, and a potential for cross protection between FHB sub-variant 1.1 in the vaccine and FHB subvariant 1.14 in the NZ98/254 strain.

Following a dose of 4CMenB given at 4 years of age, a robust response occurred, with consistently higher antibody titres in the follow-on groups compared with the 4CMenB-naïve group, indicating induction of immunological memory following vaccination at earlier time points. These data provide important information on the probable duration of protection with different vaccination schedules, which will be informative for policymakers.

Data from this study indicate the likely need for booster doses of 4CMenB in later childhood if ongoing protection is required. While booster vaccination in pre-school years may be justified because the incidence of MenB disease remains high in 1 to 4–year-old children [9], its benefit beyond pre-school years is uncertain given the much lower risk of disease during this time. In addition, the findings of previous studies [3,4] suggest that such a strategy is unlikely to provide long-term protection especially to adolescence when the next peak in disease occurs. Since the rates of MenB disease are low after 4 years of age [9], the chief aim of an early childhood vaccination programme should be to achieve the best antibody responses in the first few years of life when the burden of meningococcal disease is greatest. Furthermore, in view of the variation in epidemiology and unpredictable nature of the disease, such vaccination programmes should be aligned with regional disease epidemiology and the timing of boosters determined by need.
The loss of protective antibodies over time is not surprising and has previously been described following vaccination with 4CMenB and other meningococcal vaccines.[5,10–13] In this study, the proportion of participants with protective antibodies at baseline is similar to earlier 4CMenB phase II paediatric studies in which persistence of bactericidal antibodies to 5 years following booster vaccination was assessed in children who had received a 3+1 (2, 4, 6, 12 months) or 2+1 (6, 8, 12 months) schedule of 4CMenB at 4 years of age in this study are higher than was observed for toddlers receiving their first vaccination at 12 or 13 months.[3,4] The results contrast the findings in an adolescent study[14] where the proportion of participants with protective antibodies 18–24 months following vaccination with 2 or 3 doses of 4CMenB was much higher than observed in this study for target strains 44/76-SLand NZ98/254 but not 5/99, possibly reflecting either immunological maturation from childhood to adolescence, priming and boosting through pharyngeal carriage of meningococci or cross reactive antigens in the older age group.[15] Although based on the currently available criteria for protection, the natural decline in circulating functional antibodies following boosting in the second year of life might suggest that duration of protection over time may not be guaranteed since the majority of toddlers do not have protective antibodies against most strains, it remains unclear how well available in vitro data match duration of protection in the field. Additionally, the considerable inter-strain variation in the magnitude of decline of bactericidal antibodies makes it challenging to draw any definite conclusions regarding the clinical relevance of this decline, emphasising the importance of post-implementation surveillance to obtain direct evidence of the vaccine’s effectiveness.

In September 2015, 4CMenB vaccine was introduced into the UK immunisation programme in a 2+1 rather than a 3+1 schedule, with administration of the vaccine at 2, 4 and 12 months of age. Although this schedule has not been studied directly, data from previous studies[4,16,17] indicate that the immunogenicity of the 4MenB vaccine is not likely to be compromised by this reduced dose vaccination schedule. In addition, since the NadA protein is also found on the surface of the epidemic hypervirulent sequence type (ST) 11 meningococcal W strain which is responsible for the recent increase in the incidence of MenW disease in the UK[18–20], the introduction of 4CMenB into the UK immunisation programme will provide the unique opportunity to observe the potential impact of the vaccine on capsular group W in infants.

In this study, the safety profile of 4CMenB as a fifth dose was also assessed and found to be generally acceptable and comparable for the different study groups, irrespective of prime-boost schedule received. The most reported solicited local reaction was injection site pain, occurring in significant proportion of participants although most were mild to moderate in nature. Rates of severe pain were generally higher following a fifth dose of 4CMenB given at 4 years than with a first dose given to vaccine-naïve participants of the same age. The proportion of vaccine-naïve participants experiencing severe pain with the first vaccine dose at 4 years in this study is similar to that observed with a first dose given to vaccine-naïve participants of the same age. The proportion of vaccine-naïve participants experiencing severe pain with the first vaccine dose at 4 years in this study is similar to that observed with a first dose given to vaccine-naïve participants of the same age. The proportion of vaccine-naïve participants experiencing severe pain with the first vaccine dose at 4 years in this study is similar to that observed with a first dose given to vaccine-naïve participants of the same age.

| Table 2 | Proportion of participants (95% confidence intervals) with (i) hSBA titres ≥ 5 for each reference strain at baseline and one month after vaccination at 4 years of age and (ii) fourfold rise in hSBA titres after one dose of 4CMenB at 4 years. |
|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| 246Con12 | 246Con18 | 246Con24 | 246Lon18 | 246Lon24 | 243Con12 | 243Con14 | 243Con24 | Naïve |
| **Baseline @ 4 years** | | | | | | | | | |
| Baseline | 62/67 93% | 59/60 98% | 56/58 97% | 62/64 97% | 62/62 100% | 54/54 100% | 38/42 90% | 25/28 92% | 27/28 96% | 9/20 50% |
| One month after booster | 26/26 100% | 18/18 100% | 16/16 100% | 16/16 100% | 26/26 100% | 15/15 100% | 38/38 100% | 26/26 100% | 26/26 100% | 168/188 89% |
| Four fold rise @ one month post booster | 5/10 50% | 3/6 50% | 4/8 50% | 5/10 50% | 3/6 50% | 4/8 50% | 5/10 50% | 3/6 50% | 4/8 50% | 16/32 50% |

**Strain H44/76 (fHBP)**

<table>
<thead>
<tr>
<th>Baseline @ 4 years</th>
<th>One month after booster</th>
<th>Four fold rise @ one month post booster</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>5/67 75%</td>
<td>4/60 66%</td>
</tr>
<tr>
<td>One month after booster</td>
<td>17/26 65%</td>
<td>15/26 58%</td>
</tr>
<tr>
<td>Four fold rise @ one month post booster</td>
<td>7/26 27%</td>
<td>6/26 23%</td>
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</table>

**Strain N298/254 (OMV)**

<table>
<thead>
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<th>One month after booster</th>
<th>Four fold rise @ one month post booster</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>61/63 97%</td>
<td>5/16 31%</td>
</tr>
<tr>
<td>One month after booster</td>
<td>44/46 95%</td>
<td>3/16 19%</td>
</tr>
<tr>
<td>Four fold rise @ one month post booster</td>
<td>25/26 96%</td>
<td>14/16 88%</td>
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**Strain M10713 (NHBA)**

<table>
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<tr>
<th>Baseline @ 4 years</th>
<th>One month after booster</th>
<th>Four fold rise @ one month post booster</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>35/55 65%</td>
<td>4/17 24%</td>
</tr>
<tr>
<td>One month after booster</td>
<td>64/65 97%</td>
<td>5/16 31%</td>
</tr>
<tr>
<td>Four fold rise @ one month post booster</td>
<td>25/26 96%</td>
<td>14/16 88%</td>
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immunisation, the recommendation in the UK is for paracetamol to be routinely given at the time of immunisation with 4CMenB at 2 and 4 (but not 12) months, and two further doses to given at 4–6 monthly intervals [23]. Given the low rates of fever in this study, the use of paracetamol for this purpose is unlikely to be a requirement for immunisation at 4 years of age.

The geographical spread of the study population makes the data presented here more generalisable across different populations than previously published similar studies. Inclusion of a control group of robust sample size makes it possible to compare the post boost immunogenicity of the different schedules with that induced following a first dose administered to vaccine-naïve children at 4 years of age and strengthens interpretation of the data. Although the numbers in each study group were small, these exceed those in previous first dose trials (i.e. at baseline at 4 years and (iii) following a booster dose to toddlers. The introduction of 4CMenB in the UK represents an important milestone in the prevention of childhood meningitis and septicaemia. Data from the impact evaluation will allow effectiveness to be aligned with these data on antibody persistence and waning and will inform future policy decisions.

5. Conclusion

These data demonstrate that 4CMenB induced immunological memory when administered using different infant vaccination schedules and is immunogenic in vaccine-naïve 4-year-old children, but antibody levels wane after administration of a booster dose to toddlers. The introduction of 4CMenB in the UK represents an important milestone in the prevention of childhood meningitis and septicaemia. Data from the impact evaluation will allow effectiveness to be aligned with these data on antibody persistence and waning and will inform future policy decisions.

Financial disclosure

GSK Vaccines S.r.l. (formerly known as Novartis Vaccines and Diagnostics S.r.l.) Siena, Italy (now a member of the GSK group of companies, due to the acquisition by GSK group of companies of the non-influenza Novartis’s Vaccines division), provided the funding for this study. With the lead investigators, GSK Vaccines S.r.l. was involved in the design of the study as well as analysis of the data, review and comment on the manuscript. Data collection was undertaken by the study investigators. Editorial control of the manuscript was assigned to the University of Oxford. GSK Vaccines S.r.l. conducted the primary analysis of the data prior to being independently validated with full access to all data at the University of Oxford by M Voysey and S Jawad.

Competing interests

All authors have completed the ICMJE uniform disclosure form. M.D. Snape, A. Finn, G. Bona, S. Esposito, J. Diez-Domingo, R. Prymula act as investigators for clinical studies from both non-commercial funding bodies and commercial sponsors (i.e. some or all of Novartis Vaccines, GlaxoSmithKline, Sanofi-Aventis, Sanofi-Pasteur MSD, MedImmune and Pfizer Vaccines) conducted
on behalf of their institutions as listed in the affiliations. M.D. Snape participates in advisory boards and speaking engagements for vaccine manufacturers; all payments received are paid to their respective institutions. Before October 2014, A. Finn undertook paid consultancy and speaking engagements for vaccine manufacturers, all income was paid to his employers. Owing to his membership of the UK Department of Health’s (DH) Joint Committee on Vaccination and Immunisation (JCVI), A Finn no longer gives talks or undertakes advisory work for industry, either paid or unpaid. R. Prymula, J. Diez-Domingo, and S. Esposito also undertake consultancy and advisory work and receive speaking honoraria, travel and accommodation reimbursements for several commercial sponsors. M.A. Iro has received travel grants from GSK group of companies for attendance at conferences. The NIHR Oxford Biomedical Research Centre provides salary support for M D Snape, who is a Jenner Investigator. A J Pollard is a Jenner Investigator and James Martin Senior Fellow and has previously conducted research on behalf of Oxford University funded by vaccine manufacturers. A.J. Pollard, P.T. Heath and A. Finn do not receive any personal renumeration from vaccine manufacturers. A.J. Pollard is chair of the UK Department of Health’s (DH) Joint Committee on Vaccination and Immunisation (JCVI); the views presented in this manuscript do not necessarily represent the views of DH or JCVI. P. Dull and A. Odueyungbo were formerly employees of Novartis Vaccines and Diagnostics; D. Toneatto is current employee of GSK group of companies. M. Voysey and S. Jawad declare no competing interests.

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Drafting of the manuscript: M.A. Iro.
Critical revision of the manuscript for important intellectual content: A.J. Pollard, J. Diez-Domingo, M.D. Snape, M.A. Iro, S. Esposito, G. Bona, M. Voysey, R. Prymula, A. Finn, P. Heath, P.M. Dull, D. Toneatto, A. Odueyungbo.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.vaccine.2016.11.009.

References