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Immunogenicity of a low-dose diphtheria, tetanus and acellular pertussis combination vaccine with either inactivated or oral polio vaccine compared to standard-dose diphtheria, tetanus, acellular pertussis when used as a pre-school booster in UK children: A 5-year follow-up of a randomised controlled study

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ABSTRACT

This serological follow up study assessed the kinetics of antibody response in children who previously participated in a single centre, open-label, randomised controlled trial of low-dose compared to standard-dose diphtheria booster preschool vaccinations in the United Kingdom (UK). Children had previously been randomised to receive one of three combination vaccines: either a combined adsorbed tetanus, low-dose diphtheria, 5-component acellular pertussis and inactivated polio vaccine (IPV) (Tdap–IPV, Repevax®; Sanofi Pasteur MSD); a combined adsorbed tetanus, low-dose diphtheria and 5-component acellular pertussis vaccine (Tdap, Covaxis®; Sanofi Pasteur MSD) given concomitantly with oral polio vaccine (OPV); or a combined adsorbed standard-dose diphtheria, tetanus, 2-component acellular pertussis and IPV (DTap–IPV, Tetravac®; Sanofi Pasteur MSD). Blood samples for the follow-up study were taken at 1, 3 and 5 years after participation in the original trial (median, 5.07 years of age at year 1), and antibody persistence to each vaccine antigen measured against defined serological thresholds of protection.

All participants had evidence of immunity to diphtheria with antitoxin concentrations greater than 0.01 IU/mL five years after booster vaccination and 75%, 67% and 79% of children who received Tdap–IPV, Tdap + OPV and DTaP–IPV, respectively, had protective antitoxin levels greater than 0.1 IU/mL. Long lasting protective immune responses to tetanus and polio antigens were also observed in all groups, though polio responses were lower in the sera of those who received OPV.

Low-dose diphtheria vaccines provided comparable protection to the standard-dose vaccine and are suitable for use for pre-school booster vaccination.

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1. Introduction

Children receive multiple doses of diphtheria vaccine in the United Kingdom (UK) immunisation schedule both as diphtheria toxoid antigen (3 doses by 15 years of age) and as a mutant diphtheria toxoid protein, CRM197, a component of several protein–polysaccharide conjugate vaccines (up to 4 doses). The importance of maintaining diphtheria immunity through immunisation is emphasised by outbreaks of diphtheria where immunisation programmes break down, as seen in India [1] and Nigeria [2]. However, diphtheria toxoid causes local reactions and
for this reason, to improve tolerability without compromising protection, several vaccines have been developed containing a low-dose of the antigen in an attempt to reduce reactogenicity.

In 2001, the UK infant immunisation programme provided protection against *Haemophilus influenzae* type b (Hib), diphtheria (D), tetanus (T), pertussis with 3 doses of a whole cell pertussis (wP) combination vaccine administered in the first 4 months of life together with oral poliomyelitis vaccine (OPV). At that time, children received their first booster dose of diphtheria toxoid in combination with tetanus toxoid (with OPV and measles, mumps and rubella [MMR] vaccines; DT + OPV + MMR) before school entry and at least 3 years after completion of the infant 2-, 3- and 4-month primary course [3].

Concerns over local reactions (mainly erythema and induration) following multiple booster doses of diphtheria antigen during childhood have been raised. Although at the time of the primary study low-dose diphtheria (d) vaccine was recommended in the UK for children over the age of 10 years receiving the vaccine as part of the adolescent booster, recommendations for a low-dose diphtheria vaccine did not exist for younger children [3].

To ensure reduced reactogenicity and enhance population immunity against pertussis, acellular pertussis (aP/ap) vaccine was added to the pre-school booster in the UK in 2001; aP vaccines are preferred over wP vaccines, particularly for boosters, because they are associated with fewer local and systemic adverse events [4–6]. In 2004 inactivated polio vaccine (iPV) was introduced to replace the live OPV [7]. Unlike OPV, iPV does not carry a risk of vaccine-associated paralysis [8]. In addition, iPV can be incorporated into combination vaccines, simplifying immunisation schedules [9].

We commenced a study in 2001 comparing the immunogenicity and reactogenicity of one low-dose and one standard-dose diphtheria vaccine combined with tetanus, acellular pertussis and IPV (Tdap–IPV and DTaP–IPV) and of one low-dose diphtheria vaccine combined with tetanus and acellular pertussis and given concomitantly with OPV (Tdap + OPV) as a pre-school booster in UK children [9]. The study comprised Visit 1 (baseline blood draw and vaccination) and Visit 2 (post-vaccination blood draw 28 to 42 days later). Three hundred children, 100 children per vaccine group, were vaccinated at a mean age of 3.9 years. Full study details and results have been reported previously and showed robust immune responses following immunisation with all three vaccines at 1 month [10].

The vaccines studied (Tdap–IPV, Tdap + OPV and DTaP–IPV) were all sufficiently immunogenic for use as a pre-school booster in the UK, despite Tdap–IPV and Tdap containing a lower diphtheria dose, and could be administered concomitantly with MMR vaccine. All three combinations were well tolerated [10].

The objective of this extended follow-up study was to evaluate the persistence of immunity 1, 3 and 5 years after administration of this pre-school booster vaccine.

## 2. Methods

### 2.1. Participants and vaccines

Study visits were performed at approximately 1, 3 and 5 years after children had received one of 3 different pre-school booster vaccines at an age of 3.5–5 years in a single centre (Oxford Vaccine Group, Churchill Hospital, Oxford, UK) open-label, randomised, controlled, Phase III study.

In the original clinical trial children aged 3.5–5 years were randomly assigned to one of three study groups: a combined adsorbed tetanus, low-dose diphtheria, 5-component acellular pertussis and IPV (Tdap–IPV, Repevax®; Sanofi Pasteur MSD); a combined adsorbed tetanus, low-dose diphtheria and 5-component acellular pertussis vaccine (Tdap, Covaxis®; Sanofi Pasteur MSD) given concomitantly with OPV; or a combined adsorbed diphtheria, tetanus, 2-component acellular pertussis and IPV (DTaP–IPV, TetraVac®; Sanofi Pasteur MSD). In all groups, MMR vaccine was optionally given concomitantly.

The two low-dose diphtheria vaccines (Tdap–IPV and Tdap) contained pertactin (PRN) and fimbriae (FIM) types 2 + 3, as well as reduced quantities of pertussis toxoid (PT) and filamentous haemagglutinin (FHA). The standard-dose diphtheria vaccine (DTaP–IPV) contained only PT and FHA (Table 1).

All children vaccinated in the initial study and who had not been excluded or withdrawn were eligible for inclusion in the follow-up study.

The objective of the follow-up study was to evaluate the persistence of antibodies to the vaccine antigens (diphtheria, tetanus, PT, FHA, PRN, FHM, and poliomyelitis types 1, 2, and 3) 1, 3, and 5 years after receipt of the study vaccines. The 1 year visit occurred between January and November 2003, year 3 between December 2004 and November 2005 and year 5 between January and November 2007, 60 to 63 months after the date of the original study vaccine administration.

At each visit a 5.0 mL sample of venous blood was obtained; participation at each timepoint was optional and non-participation at one timepoint was not an exclusion criterion for future participation. No vaccines were administered as part of the follow-up study, although anyone identified as having low antibody levels to a particular antigen were advised to receive a further dose of the appropriate vaccine.

### Table 1

<table>
<thead>
<tr>
<th>Antigen concentrations of Tdap–IPV, Tdap + OPV and DTaP–IPV.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tdap–IPV</strong></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Purified tetanus toxoid</td>
</tr>
<tr>
<td>Purified diphtheria toxoid</td>
</tr>
<tr>
<td>Purified pertussis toxoid (PT)</td>
</tr>
<tr>
<td>Purified filamentous haemagglutinin (FHA)</td>
</tr>
<tr>
<td>Purified fimbriae types 2 + 3 (FIM)</td>
</tr>
<tr>
<td>Purified pertactin (PRN)</td>
</tr>
<tr>
<td>Inactivated poliomyelitis virus type 1</td>
</tr>
<tr>
<td>Inactivated poliomyelitis virus type 2</td>
</tr>
<tr>
<td>Inactivated poliomyelitis virus type 3</td>
</tr>
<tr>
<td>Live attenuated type 1 poliovirus</td>
</tr>
<tr>
<td>Live attenuated type 2 poliovirus</td>
</tr>
<tr>
<td>Live attenuated type 3 poliovirus</td>
</tr>
</tbody>
</table>

**Abbreviations:** Tdap–IPV: combined adsorbed tetanus, low-dose diphtheria, 5-component acellular pertussis and inactivated polio vaccine (Repevax®; Sanofi Pasteur MSD); Tdap + OPV: combined adsorbed tetanus, low-dose diphtheria and 5-component acellular pertussis vaccine (Covaxis®; Sanofi Pasteur MSD) given concomitantly with oral polio vaccine; DTaP–IPV: combined adsorbed standard-dose diphtheria, tetanus, 2-component acellular pertussis and inactivated polio vaccine (TetraVac®; Sanofi Pasteur MSD).
The study was conducted in accordance with the principles of the Declaration of Helsinki and had the approval of the Oxfordshire Research Ethics Committee (C01.183). Signed, informed consent was obtained from a parent at each study visit prior to any procedure being performed. Verbal agreement was obtained from the participant.

2.2. Immunogenicity and safety assessments

Immune responses were measured by seroneutralisation (SN) for diphtheria and poliovirus antigens and by enzyme immunoassays (EIA) for tetanus and pertussis antigens (PT, FHA, PRN and FIM). Seroprotection was defined as a diphtheria antibody titre (SN) ≥ 0.1 IU/mL; tetanus antibody titre (EIA) ≥ 0.1 IU/mL; and poliovirus types 1, 2 and 3 antibody titre (SN) ≥ 8 (1/dilution), respectively. In addition to seroprotection rates, basic clinical immunity to diphtheria and tetanus were defined as an antibody titre ≥ 0.01 IU/mL. In the absence of an agreed correlate of protection, no thresholds of response for pertussis antigens were defined but GMCs were calculated.

Samples obtained at year 1 were analysed in Aventis Pasteur laboratories in Canada. From year 3 onwards all assays were performed by the Global Clinical Immunology platform of Sanofi Pasteur Inc. (Swiftwater, PA, USA) In order to compare the results obtained at year 1 with those obtained at year 3 an year 5, laboratory concordance studies were performed. As a consequence, conversion factors were applied for the results of diphtheria, tetanus and polioimmunity types 1 and 2 at year 1 but this was deemed not necessary for the other valences, i.e. for type 3 polioimmunity and pertussis.

No safety assessments were carried out during the follow-up study as no vaccines were given. Only serious adverse events related to the blood sampling process were recorded.

2.3. Statistics

The immunogenicity endpoints for 5-year post-booster persistence were basic clinical immunity and seroprotection rates for diphtheria, tetanus and type 1, 2 and 3 poliovirus antigens. Immunogenicity analyses were performed for the intention-to-treat (ITT) population. The ITT population at the 5-year visit comprised all children included in the ITT population in the primary study who had a blood sample at year 5. In addition, the antibody data at year 1 and year 3, are also presented for the sub-population of participants included in the ITT population at year 5.

Geometric mean antibody concentrations/titres (GMCs/GMTs), and their 2-sided 95% confidence intervals (CIs) were calculated for immunogenicity criteria. In addition, the proportions of participants with antibody concentrations/titres against pre-defined accepted thresholds were calculated.

The sample size was calculated for the primary study. Only descriptive statistical analyses were performed in the follow-up study, which was not powered for antibody persistence. No hypotheses relating to expected response rates were formulated.

3. Results

3.1. Study population

Randomisation and follow-up of children is shown in Fig. 1. In total, of the 300 children who were enrolled into the initial study, 219 children participated at year 1 (73.0%), 161 (53.7%) at year 3 and 146 (48.7%) at year 5. 140 children were included in the ITT population at year 5. A subset of these children also had results available at year 1 (n = 117) and year 3 (n = 113) and are therefore included in this analysis.

At year 1 children were aged between 4.51 and 6.18 years (mean age 5.07), year 3 aged between 6.50 and 8.09 (mean age 7.08 years) and at year 5, children were aged between 8.56 and 10.13 years.
(mean age: 9.06 years). At all 3 timepoints age of participant was similar among the three groups. Throughout the study slightly more girls participated than boys (Table 2).

### 3.2. Antibody persistence

Antibody levels were lower at the first visit in this study (year 1) than they had been at 1 month after vaccination in the initial study [10]. Five years after receipt of vaccine all participants had diphtheria antitoxin concentrations ≥0.01 IU/mL. Furthermore, 75.00%, 66.67% and 78.95% of children who received Tdap–IPV, Tdap + OPV and DTap–IPV, respectively, maintained protective antibody levels for diphtheria concentrations ≥0.1 IU/mL (Table 3).

All participants had tetanus antitoxin titres ≥0.01 IU/mL; 100%, 96.30% and 89.47% of children who received Tdap–IPV, Tdap + OPV and DTap–IPV, respectively, had titres ≥0.1 IU/mL at the 5 year follow up visit (Table 3). Tetanus GMCs were slightly lower in the DTap–IPV group than in the other 2 groups at all timepoints but CIs overlapped except at year 5 (Table 3).

Five years after receipt of the pre-school vaccine(s), seroprotection rates for type 1 poliomyelitis were 97.87%, 96.23% and 100% for Tdap–IPV, Tdap + OPV and DTap–IPV, respectively. All participants had a titre of ≥1.8 for type 2 poliomyelitis in the three vaccine groups. Seroprotection rates for type 3 poliomyelitis were 95.74% (45/47 children) and 97.37% (37/38 children) for Tdap–IPV and DTap–IPV, respectively. In contrast, 9 children out of 53 did not reach the threshold in the Tdap + OPV group, corresponding to a seroprotection rate of 83.02% (Table 4). Polio GMTs were lower at all timepoints in the OPV group than in the IPV groups (Table 4).

Persisting antibody responses against pertussis antigens were observed in all groups for PT and FHA and also for PRN and FIM in the Tdap–IPV and Tdap + OPV groups as these antigens are not contained in the DTaP–IPV vaccine (Table 5).

During the initial study 2 participants that received the Tdap + OPV vaccines were identified as not having achieved protective antibody levels either for diphtheria or for polio. The relevant booster vaccine was administered and the individual with low polio titres, who participated at all 3 follow-up visits, was not included in the polio analysis and the individual with low diphtheria antibody levels, who participated at the 1 year timepoint, was not included in the diphtheria and tetanus analysis. At year 3, three years after receipt of the DTaP–IPV vaccine, one participant had not maintained protective antibody levels for diphtheria and was advised to receive a booster dose of vaccine and did not participate at the 5 year timepoint.

There were no serious adverse events associated with the blood sampling procedure carried out at any of the 3 follow up visits.

### 4. Discussion

This study reports on the persistence of antibody up to 5 years following receipt of one of 3 pre-school booster vaccinations

### Table 2

Demographic characteristics (intention-to-treat population at each Visit).

<table>
<thead>
<tr>
<th>Year</th>
<th>Tdap–IPV</th>
<th>Tdap + OPV</th>
<th>DTap–IPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
<td>Min–Max</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>1</td>
<td>5.11 (0.38)</td>
<td>4.54–6.18</td>
<td>5.05 (0.32)</td>
</tr>
<tr>
<td>3</td>
<td>7.1 (0.35)</td>
<td>6.69–8.01</td>
<td>7.06 (0.33)</td>
</tr>
<tr>
<td>5</td>
<td>9.07 (0.37)</td>
<td>8.59–9.96</td>
<td>9.05 (0.27)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>n(%)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31 (44.93%)</td>
<td>30 (40.00%)</td>
<td>39 (54.17%)</td>
</tr>
<tr>
<td>3</td>
<td>20 (42.55%)</td>
<td>21 (35.00%)</td>
<td>24 (51.06%)</td>
</tr>
<tr>
<td>5</td>
<td>21 (43.75%)</td>
<td>18 (33.33%)</td>
<td>21 (55.26%)</td>
</tr>
</tbody>
</table>
Table 4
Antibody responses to poliovirus types 1, 2, and 3 at 1, 3, and 5 years after a booster dose of Tdap–IPV, Tdap + OPV or DTap–IPV (intention-to-treat population at year 5).

<table>
<thead>
<tr>
<th>Time post booster</th>
<th>Tdap–IPV</th>
<th>Tdap + OPV</th>
<th>DTap–IPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>1 Year</td>
<td>3 Year</td>
</tr>
<tr>
<td>Polio 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% ≥ 1:8 [95% CI]</td>
<td>100%</td>
<td>90.59–100</td>
<td>100%</td>
</tr>
<tr>
<td>GMT [95% CI]</td>
<td>338.74</td>
<td>267.04–429.69</td>
<td>284.59</td>
</tr>
<tr>
<td>Polio 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% ≥ 1:8 [95% CI]</td>
<td>100%</td>
<td>90.59–100</td>
<td>100%</td>
</tr>
<tr>
<td>GMT [95% CI]</td>
<td>471.59</td>
<td>356.21–624.35</td>
<td>341.72</td>
</tr>
<tr>
<td>Polio 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% ≥ 1:8 [95% CI]</td>
<td>100%</td>
<td>90.59–100</td>
<td>100%</td>
</tr>
</tbody>
</table>

Abbreviations: CI: confidence interval; GMT: geometric mean titres. Tdap–IPV: combined adsorbed tetanus, low-dose diphtheria, 5-component acellular pertussis and inactivated polio vaccine (Repevax®; Sanofi Pasteur MSD); Tdap + OPV: combined adsorbed tetanus, low-dose diphtheria and 5-component acellular pertussis vaccine (Covavax®; Sanofi Pasteur MSD) given concomitantly with oral polio vaccine; DTap–IPV: combined adsorbed standard-dose diphtheria, tetanus, 2-component acellular pertussis and inactivated polio vaccine (Tetravac®; Sanofi Pasteur MSD).

Table 5
Geometric mean concentrations of pertussis antibodies at 1, 3 and 5 years after a booster dose of Tdap–IPV, Tdap + OPV or DTap–IPV (intention-to-treat population at year 5).

<table>
<thead>
<tr>
<th>Time post booster</th>
<th>Tdap–IPV</th>
<th>Tdap + OPV</th>
<th>DTap–IPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>1 Year</td>
<td>3 Year</td>
</tr>
<tr>
<td>PT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FHA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIM</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PT: pertussis toxoid; FHA: filamentous haemagglutinin; PRN: pertactin; FIM: fimbriae types 2 + 3; CI: confidence interval; GMC: geometric mean concentrations. Abbreviations: PT: pertussis toxoid; FHA: filamentous haemagglutinin; PRN: pertactin; FIM: fimbriae types 2 + 3; CI: confidence interval; GMC: geometric mean concentrations. Tdap–IPV: combined adsorbed tetanus, low-dose diphtheria, 5-component acellular pertussis and inactivated polio vaccine (Repevax®; Sanofi Pasteur MSD); Tdap + OPV: combined adsorbed tetanus, low-dose diphtheria and 5-component acellular pertussis vaccine (Covavax®; Sanofi Pasteur MSD) given concomitantly with oral polio vaccine; DTap–IPV: combined adsorbed standard-dose diphtheria, tetanus, 2-component acellular pertussis and inactivated polio vaccine (Tetravac®; Sanofi Pasteur MSD).
administered in a clinical trial of children aged 3.5 to 5 years in 2001. Following a rapid decline in the first year for all antibodies [10], the data from this study demonstrate that a low-dose diphtheria toxoid-containing vaccine (Tdap–IPV and Td) provides long-lasting immune responses for all antigens with levels of immunity being broadly similar to those achieved with standard-dose diphtheria toxoid vaccines (DTaP–IPV). All 3 vaccines studied in the primary study are suitable for use as a pre-school booster to provide a fourth dose of the contained antigens.

Overall there were slightly more females than males in the study but this reflected the original study population (55% versus 45%). 300 children participated in the initial study of which 219, 161 and 146 participated at 1, 3 and 5 years, respectively. The retention rate is not dissimilar to other studies conducted in cohorts of children in Oxford (unpublished observations). By the 5-year time point it was known that several families had moved away from the area but reasons for non-participation amongst the remaining children are largely unknown. A separate qualitative study, conducted with the cohort of children approached for the initial vaccine study, identified anxiety of blood sampling and temperament of child as reasons for non-participation [11]. While these views were expressed in relation to a study involving a new vaccine it is likely the issues remain relevant when making a decision whether or not to participate in a study involving just a blood sample.

The proportion of children maintaining persistence of antibodies above accepted seroprotection levels for diphtheria, tetanus, and poliomyelitis were similar to those reported in a previous study, in which seroprotective antibody levels against diphtheria, tetanus, types 1–3 poliomyelitis and Hib were maintained 4–5 years after primary vaccination and a first booster with the DTaP–IPV–Hib vaccine Pentavac® [12]. Furthermore, while a German study demonstrated that diphtheria antitoxin titres wane over the first year following vaccination irrespective of the initial titre, it has been suggested that the protection afforded by low-dose diphtheria containing combinations may still persist through to adolescence [13]. This follow-up study supports lasting protection against diphtheria for up to 5 years following receipt of a pre-school booster vaccine. It is noteworthy that, although the point estimates for the low dose diphtheria vaccine-induced anti-toxin concentrations are slightly lower at each timepoint than the standard dose vaccine levels, none of these concentrations were significantly different as confidence intervals overlapped substantially.

While there were widely accepted reference levels for full protection against diphtheria (antitoxin concentrations ≥0.1 IU/mL) [14] and tetanus (antitoxin concentrations ≥0.1 IU/mL) [15] there remain no clear serological correlates of protection for pertussis from large scale field studies, which makes it difficult to interpret the immunogenicity of the pertussis components of the vaccines in the original study [10]. Antibodies to PT, FHA, PRN and FIM were therefore measured by EIA using in-house reference standards. Despite some waning, the data from the study show persistence of antibody responses against PT and FHA pertussis antigens in all groups and also for PRN and FIM in the 2 groups that received a 5-component acellular pertussis vaccine.

As the study was not powered to show any intergroup statistical differences a comparative analysis of results across the three treatment groups in this follow-up antibody persistence study was not attempted. However, serum polio responses were more robust in the groups receiving IPV than the OPV group at almost all time points (non-overlapping CIs). Since mucosal responses were not measured, differences in protection induced by these different vaccine strategies cannot be determined. We also noted that the there is a rise in some of the pertussis antibody concentrations between the 3 and 5 year timepoints, which we propose may reflect natural boosting.

In conclusion, a pre-school booster vaccine containing a low-dose diphtheria toxoid (Tdap–IPV or Tdap+OPV) demonstrates comparable persistent immunity for diphtheria, tetanus and pertussis antigens to a standard-dose diphtheria toxoid vaccine (DTaP–IPV) 5 years after administration to children aged as young as 3.5 years living in the UK.

Funding and conflict of interest statement

The study was sponsored by Sanofi Pasteur MSD. With the exception of the authors employed by Sanofi Pasteur MSD (M.B, P.R, A.F and N.K), no authors have received direct payment from Sanofi Pasteur MSD. The sponsor funded the study and developed the study protocol in collaboration with A.J.P. Employees of the sponsor reviewed the manuscript before submission for publication. Development of this manuscript was also supported by the Oxford Partnership Comprehensive Biomedical Research Centre with funding from the NIHR Biomedical Research Centre Programme (T.J). A.J.P. has previously acted as chief investigator for clinical trials conducted on behalf of Oxford University, sponsored by vaccine manufacturers including Sanofi Pasteur MSD.

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