

## Immunogenicity and safety of an acellular pertussis, diphtheria, tetanus, inactivated poliovirus, Hib-conjugate combined vaccine (Pentaxim™) and monovalent hepatitis B vaccine at 6, 10 and 14 weeks of age in infants in South Africa

Shabir Ahmed Madhi, Clare Cutland, Stephanie Jones, Michelle Groome, Esteban Ortiz

**Objective.** To assess the immunogenicity and safety data for a pentavalent combination vaccine containing acellular pertussis, inactivated poliovirus, and *Haemophilus influenzae* (Hib) polysaccharide-conjugate antigens.

**Methods.** A DTaP-IPV//PRP~T vaccine (Pentaxim™) was given at 6, 10 and 14 weeks of age to 212 infants in South Africa. Monovalent hepatitis B vaccine was given concomitantly.

Immunogenicity was assessed using seroprotection and seroconversion rates; safety was assessed by monitoring for solicited injection site and systemic adverse events, and follow-up monitoring for unsolicited adverse events and serious adverse events.

**Results.** Immunogenicity was high for each vaccine antigen, and similar to a reference study done in France using a similar (2, 3 and 4 months of age) administration schedule. After the third dose, 94.6% of participants had anti-PRP  $\geq 0.15$   $\mu\text{g/ml}$ .

The anti-PRP geometric mean antibody titre (GMT) was 2.0  $\mu\text{g/ml}$ . The seroprotection rates for diphtheria and tetanus ( $\geq 0.01$  IU/ml), poliovirus types 1, 2 and 3 ( $\geq 8$  1/dil U) and hepatitis B were all 100%. Anti-polio GMTs were very high, 1 453, 1 699 and 2 398 (1/dil U) for types 1, 2 and 3, respectively. The seroconversion/vaccine response rates to pertussis antigens (4-fold increase in antibody concentration) were 97.5% for PT and 83.9% for FHA.

**Conclusions.** The DTaP-IPV//PRP~T vaccine was highly immunogenic at 6, 10 and 14 weeks of age in infants in South Africa, was compatible with the monovalent hepatitis B vaccine, and was well tolerated.

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Vaccines are cost-effective public health tools to prevent and control infectious diseases. Their routine use has had enormous impact on diseases such as tetanus, diphtheria, pertussis, poliomyelitis and *Haemophilus influenzae* type b (Hib).<sup>1-5</sup> Vaccines combining inactivated whole-cell *Bordetella pertussis* antigens with diphtheria and tetanus toxoids (DTwP) have been used for over 60 years and have been central to the World Health Organization (WHO) Expanded Program of Immunization (EPI) since 1974.

Safety and reactogenicity concerns of whole-cell pertussis (wP) vaccines led to the development of acellular pertussis (aP) vaccines, comprising purified *B. pertussis* antigens. These aP vaccines are better tolerated than wP vaccines, their protective efficacy has been shown in trials, and their use is supported by the WHO.<sup>2,6-10</sup> aP vaccines are used in widespread national immunisation programmes and have been introduced in South Africa through a pentavalent combined vaccine.

The Sabin oral polio vaccine (OPV) has been successful in eliminating poliomyelitis, although replication of live attenuated polioviruses following vaccination can generate mutated viruses with renewed neurovirulence: vaccine-associated paralytic poliomyelitis

(VAPP) and vaccine-derived polioviruses (VDPVs) are rare risks of OPV.<sup>11,12</sup> In South Africa, polio vaccine-derived viruses have been detected in stool specimens of immunodeficient children,<sup>11</sup> and in sewage and river water.<sup>13</sup> Once wild poliovirus transmission has been interrupted OPV will be the only cause of poliomyelitis. In this context the use of inactivated poliovirus vaccines (IPVs) is important, there being no associated risk of VAPP or VDPVs.

The number of vaccines licensed and recommended for use in infants and children continues to increase. Incorporating multiple individual vaccines into combinations can simplify vaccine administration programmes and the inclusion of new antigens into immunisation schedules. Combination vaccines are an important advance in delivering vaccines to infants, helping to achieve high vaccination coverage and minimising costs.<sup>14-16</sup>

We assessed the immunogenicity and safety of the DTaP-IPV//PRP~T vaccine given with concomitant hepatitis B vaccination at 6, 10 and 14 weeks of age (EPI schedule) in South Africa.

### Methods

#### Study design and participants

This was a phase III, open clinical trial at Chris Hani Baragwanath Hospital, Johannesburg. Participants received three doses of DTaP-IPV//PRP~T combined vaccine and of monovalent recombinant hepatitis B vaccine following the EPI schedule of administration (6, 10 and 14 weeks of age) (clinicaltrials.gov ID NCT00254969). The protocol was approved by the University of the Witwatersrand Human Subjects Research Ethics Committee and the Medicines Control Council (MCC). Parents or legal guardians gave written informed consent before trial inclusion.

Healthy full-term ( $\geq 37$  weeks) infants with a birth weight  $\geq 2$  500 g were eligible to participate and were sequentially screened and enrolled during the first 24 hours of life. Infants were excluded at screening or before the first vaccination at 6 weeks of age if they had already received a dose of OPV or if the mother was known to be seropositive for hepatitis B virus or HIV. In South Africa a dose

Vaccine Preventable Diseases, Department of Science and Technology/National Research Foundation, and MRC Respiratory and Meningeal Pathogens Research Unit, University of the Witwatersrand, Johannesburg

Shabir Ahmed Madhi, MD  
Clare Cutland, MD  
Stephanie Jones, MD  
Michelle Groome, MD

Sanofi Pasteur, Lyon, France  
Esteban Ortiz, MD

Corresponding author: E Ortiz (esteban.ortiz@sanofipasteur.com)

of OPV is routinely given at birth, but for participating infants the first polio vaccination (IPV) was given at 6 weeks of age. At the time no published clinical data were available for this combined vaccine given at 6, 10 and 14 weeks of age. Data from a study using the same vaccine and a similar (2, 3 and 4 months of age) schedule in France were therefore used as a historical reference.<sup>17</sup>

Major exclusion criteria were acute febrile illness on the day of screening; any vaccination except BCG before trial participation; participation/planned participation in another clinical trial; receipt of blood or blood products; thrombocytopenia/bleeding disorder contraindicating intramuscular vaccination; a history of seizures; congenital/acquired immunodeficiency or immunosuppressive therapy; known systemic hypersensitivity to any of the vaccine components; or a history of a life-threatening reaction to the trial vaccine or a vaccine containing the same substances. Infants who were screened and not included were referred to their local clinic for care and were offered vaccinations according to the national recommendations.

### Vaccines

Each 0.5 ml dose of the combined DTaP-IPV//PRP~T vaccine (Pentaxim™, Sanofi Pasteur, France, batch number Z2044-1 contained  $\geq 30$  IU diphtheria toxoid,  $\geq 40$  IU tetanus toxoid, 25  $\mu$ g pertussis toxoid, 25  $\mu$ g filamentous haemagglutinin, 40 U inactivated type 1 poliovirus, D antigen, 8 U inactivated type 2 poliovirus, D antigen, 32 U inactivated type 3 poliovirus, D antigen, and 10  $\mu$ g *H. influenzae* type b polysaccharide covalently bound to tetanus toxoid (PRP~T). The PRP~T antigen was supplied as a freeze-dried powder and was rehydrated with an injectable suspension of DTaP-IPV vaccine at the time of injection. The combined vaccine was administered intramuscularly aseptically into the anterolateral aspect of the right upper thigh. The recombinant hepatitis B vaccine (Heberbiovac HB®, Biovac South Africa Ltd) was commercially available in South Africa at the time of the study. Each 0.5 ml dose contained 10  $\mu$ g of recombinant hepatitis B surface antigen (HBsAg). The hepatitis B vaccine was administered intramuscularly aseptically into the anterolateral aspect of the left upper thigh.

### Safety and reactogenicity

Participants were monitored for adverse reactions in the 30 minutes following each vaccine injection. Parents or legal guardians recorded time of onset, duration and severity of solicited injection site (tenderness, redness, swelling) and systemic (axillary temperature  $\geq 37.4^\circ\text{C}$ , vomiting, abnormal crying, drowsiness, loss of appetite, irritability) reactions on diary cards for the following 7 days. All solicited events were considered to be related to the vaccination, and any event related to vaccination was termed a 'reaction'. Unsolicited adverse events were recorded from each vaccination until the following study visit. Serious adverse events (SAEs) were recorded throughout the trial and for 6 months after the final vaccination.

### Serology

Blood samples were taken before the first dose and 1 month after the third dose. Immunological assays were performed at the Sanofi Pasteur Global Clinical Immunology Platform Laboratory in the USA, except for PRP, which was analysed by the Health Protection Agency, UK, using an enzyme-linked immunosorbent assay (ELISA). Anti-diphtheria and anti-tetanus, anti-PT and anti-FHA antibody titres were also measured by ELISA; anti-HBsAg titres were measured by VITROS chemoluminescence (ECi)/ECiQ Immunodiagnostic System; and anti-poliovirus type 1, 2 and 3 antibody titres (1/dil) were measured by microneutralisation. The pre-defined antibody levels for seroprotection (SP) were: anti-diphtheria  $\geq 0.01$  IU/ml; anti-tetanus

$\geq 0.01$  IU/ml; anti-poliovirus  $\geq 8$  reciprocal dilution (1/dil); anti-PRP  $\geq 0.15$   $\mu$ g/ml; and anti-HBsAg  $\geq 10$  mIU/ml. Since there are no accepted correlates of seroprotection for pertussis antibodies, seroconversion (SC) for anti-PT and anti-FHA was defined as a  $\geq 4$ -fold increase in antibody concentration after primary vaccination.

### Statistical methods

Our main objective was to determine the seroprotection rates for diphtheria, tetanus, poliovirus types 1, 2 and 3, and PRP and the seroconversion rates for PT and FHA 1 month after the three-dose primary vaccination. We also determined the hepatitis B seroprotection rate, antibody titres to all vaccine antigens following priming, and the safety and reactogenicity of the study vaccines. The statistical analysis was descriptive. The sample size was chosen to give sufficient precision to allow a non-inferential comparison, based on 95% confidence intervals (CIs), with the results of a previous study in France in 212 infants with the same combined vaccine given in a similar administration schedule.<sup>17</sup> The sample size was therefore set at 212 participants, ensuring at least 180 evaluable participants assuming a 15% drop-out rate.

SP and SC rates were calculated with their 95% CIs by the Clopper-Pearson exact binomial method. Geometric mean antibody titres (GMTs) were calculated with their 95% CIs using the normal approximation method. Reverse cumulative distribution curves (RCDCs) were constructed for each antibody response. Infants who received at least one dose of vaccine and had at least one antibody titration available after primary immunisation and no protocol deviations were included in the immunogenicity analysis. All participants who received at least one dose of study vaccine were included. To evaluate reactogenicity, the number and percentage of participants with solicited symptoms after each dose of vaccine were calculated.

## Results

### Participant disposition

Of 300 participants, 88 (29.3%) discontinued between consent being given at birth and the administration of the first dose of vaccine at 6 weeks of age (Fig. 1). The main reasons for non-inclusion were voluntary withdrawal not due to an adverse event (47, 53.4%) and loss to follow-up (26, 29.5%). Six (6.8%) of the 88 discontinued participants were not compliant with the study protocol, and 9 (10.2%) were screened but not included because the planned number of participants had been reached and received the standard of care and vaccinations according to the national recommendations and their physician's clinical judgement.

As planned, 212 participants received the first dose of vaccine; 50.5% were male, the mean age was 43.2 days (standard deviation (SD) 1.6 days) (approximately 6.2 weeks), and the mean weight was 3 200 g (SD 400 g). The primary vaccination phase was completed by 207 participants (97.6%) (Fig. 1). Three of the 5 who discontinued were withdrawn because of non-compliance with the protocol, one was lost to follow-up, and one discontinued because of an SAE (fatal dehydration and gastro-enteritis unrelated to vaccination).

### Immunogenicity

The SP/SC rates were high for each antigen after completion of the three-dose primary series and were similar to the historical data (Table 1). All participants were seroprotected against diphtheria ( $\geq 0.01$  IU/ml), tetanus ( $\geq 0.01$  IU/ml), poliovirus types 1, 2, and 3 ( $\geq 8$  (1/dil)) and hepatitis B ( $\geq 10$  mIU/ml); 94.6% of participants had anti-PRP titres  $\geq 0.15$   $\mu$ g/ml. The SC rates ( $\geq 4$ -fold increase in antibody titres) for pertussis antigens were 97.5% and 83.9% for PT and FHA, respectively. Overall, the SP/SC rates were similar to the reference

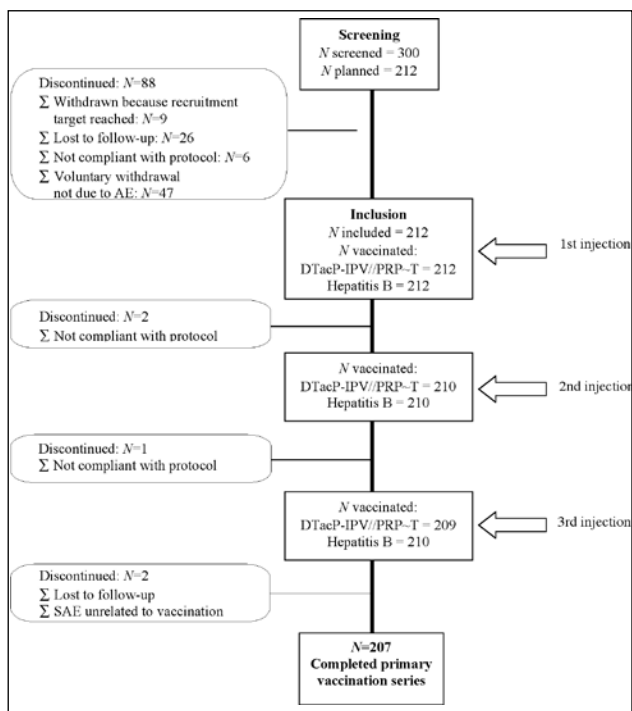


Fig. 1. Participant disposition.

study. Post-priming GMTs were high (Table II). There were marked increases in anti-PT and anti-FHT GMTs from pre-dose 1 to post-dose 3. The GMT ratios (GMTRs) were 53.5 for PT and 16.8 for FHA. All study participants had post-priming anti-PT and anti-FHA  $\geq 25$  EU/ml. Anti-PT and FHA antibody titres are graphically described using RCDCs in Fig. 2, which shows strong, linear increases in antibody titre following primary series vaccination.

**Reactogenicity and safety**

**Solicited reactions**

Table III summarises solicited symptoms after any dose of study vaccine. Reactogenicity was low for the combined and the hepatitis B vaccine. Most solicited injection site reactions occurred within 3 days after vaccination, were mild to moderate in severity, and resolved within 8 days. The most frequent injection site reactions

**Table II. Geometric mean titres (GMTs) for all vaccine antigens 1 month after the third dose of combined vaccine injection**

	GMT (95% CI)
Anti-diphtheria (IU/ml (ELISA))	0.9 (0.8 - 1.0)
Anti-tetanus (IU/ml (ELISA))	0.8 (0.7 - 0.9)
Anti-polio 1 (1/dil (seroneutralisation))	1 453.0 (1 235.9 - 1 708.3)
Anti-polio 2 (1/dil (seroneutralisation))	1 699.1 (1 410.9 - 2 046.3)
Anti-polio 3 (1/dil (seroneutralisation))	2 398.2 (1 979.8 - 2 905.0)
Anti-PRP ( $\mu$ g/ml (ELISA))	2.0 (1.6 - 2.5)
Anti-PT (EU/ml (ELISA))	382.6 (353.1 - 414.6)
Anti-FHA (EU/ml (ELISA))	161.0 (145.9 - 177.6)
Anti-HBs (mIU/ml (RIA))	929.2 (786.4 - 1 098.0)

were tenderness, swelling and erythema, with severe tenderness after only 0.6% of doses (4/628); severe swelling or erythema were not reported. The most frequently reported solicited systemic reactions were abnormal crying and irritability. Severe systemic reactions were reported after 0.5 - 1.3% of injections.

**Unsolicited reactions**

Two participants (0.9%) reported unsolicited injection site reactions. One experienced tenderness and erythema at the injection site of the combined vaccine and tenderness at the hepatitis B vaccine injection site that started more than 8 days after the second injection. The other had bruising at the combined vaccine injection site. Unsolicited systemic events were reported by 155 participants (73.1%). Most were diagnoses commonly seen in infants. Only 8 of the 155 participants reported an unsolicited systemic event assessed as related to vaccination (diarrhoea, gastro-enteritis, lower respiratory tract infection, otitis media, rhinitis, tonsillitis and generalised rash), but none was severe. No cases of hypotonic hyporesponsive episode or seizure were reported.

**Table I. Seroprotection/seroconversion vaccine response rates 1 month after three-dose primary vaccination**

	Historical reference DTaP-IPV//PRP~T* (% (95% CI))	Study vaccines DTaP-IPV//PRP~T + HB	
		n/N	% (95% CI)
Anti-diphtheria $\geq 0.01$ IU/ml (ELISA)	100 (95.9 - 100)	206/206	100.0 (98.2 - 100.0)
Anti-tetanus $\geq 0.01$ IU/ml	100 (95.9 - 100)	206/206	100.0 (98.2 - 100.0)
Anti-polio 1 $\geq 8$ (1/dil)	97.0 (91.5 - 99.4)	206/206	100.0 (98.2 - 100.0)
Anti-polio 2 $\geq 8$ (1/dil)	100 (96.4 - 100)	206/206	100.0 (98.2 - 100.0)
Anti-polio 3 $\geq 8$ (1/dil)	99.0 (94.6 - 100)	202/202	100.0 (98.2 - 100.0)
Anti-PRP $\geq 0.15$ $\mu$ g/ml	98.0 (93.0 - 99.8)	194/205	94.6 (90.6 - 97.3)
Anti-PT titre $\geq 4$ -fold increase EU/ml	89.6 (81.7 - 94.9)	192/197	97.5 (94.2 - 99.2)
Anti-FHA titre $\geq 4$ -fold increase EU/ml	89.5 (81.5 - 94.8)	172/205	83.9 (78.1 - 88.7)
Anti-HBs $\geq 10$ mIU/ml	NA	196/196	100.0 (98.1 - 100.0)

\*Data from administration of the same vaccine in a 2, 3 and 4 months of age schedule in France.<sup>17</sup>  
CI = confidence interval; ELISA = enzyme-linked immunosorbent assay; NA = not available.

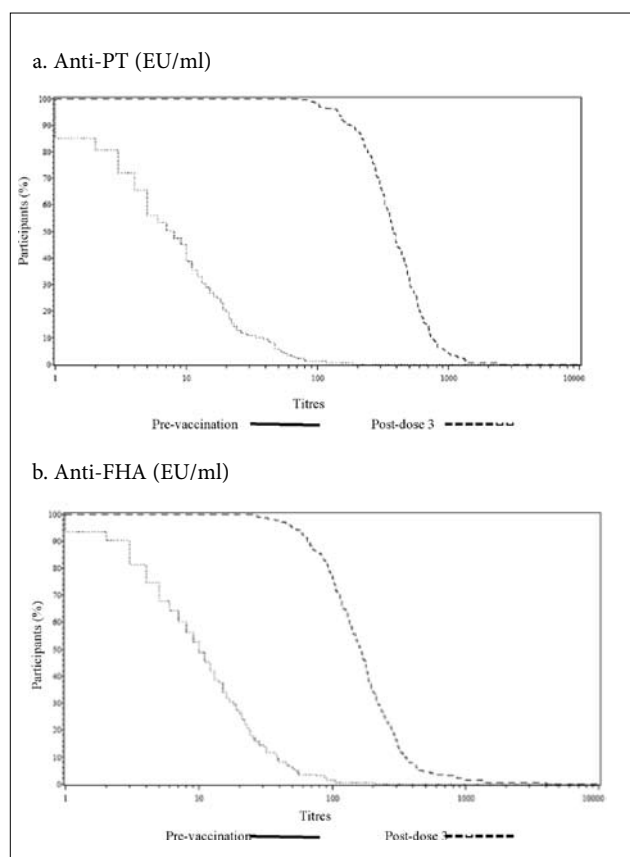


Fig. 2. Reverse cumulative distribution curves before and after primary vaccination for anti-PT and anti-FHA.

Twenty participants experienced 22 SAEs; none was considered to be related to vaccination. Of the 2 deaths, one resulted from gastro-enteritis diagnosed about a month after the third dose, followed, during hospitalisation, by dehydration with acidosis and herbal intoxication. The second fatality resulted from gastro-enteritis diagnosed about 4 months after the third dose. The remaining 18 participants with SAEs (bronchopneumonia, gastro-enteritis, bronchiolitis, epilepsy) recovered with treatment.

There was no case of litigation for any solicited reaction, unsolicited event or SAE.

### Discussion

This study assessed the immunogenicity and safety of a DTaP-IPV//PRP~T combination vaccine for primary vaccination at 6, 10 and 14 weeks of age, given concomitantly with a stand-alone recombinant hepatitis B vaccine to infants in South Africa. This combined vaccine was first licensed in 1997 in Europe and contains antigens that are well known as stand-alone vaccines. The PRP~T component is licensed as ActHIB™ and the IPV component as Imovax Polio™.<sup>18</sup>

This was compared with historical data following a 2, 3 and 4 months administration schedule,<sup>17</sup> which was used rather than 6, 10 and 14 weeks data from the Philippines<sup>19</sup> and India<sup>20</sup> because the latter were not available when our protocol was developed. The study therefore shows that the DTaP-IPV//PRP~T combined vaccine elicits strong immune responses following primary vaccination with the EPI-recommended 6, 10 and 14 weeks of age schedule, comparable with the historical data.

The safety and immunogenicity of the antigens included in the DTaP-IPV//PRP~T study vaccine have been shown in clinical studies in Europe, North and South America, Africa and Asia.<sup>19-24</sup>

Table III. Percentage of vaccine injections followed by a solicited injection site or systemic adverse reaction within 7 days after any dose

	DTaP-IPV//PRP~T (% (95% CI)) (z=628)	Hepatitis B (% (95% CI)) (z=628)
<b>Injection site reactions</b>		
Overall		
Any	57.5 (53.5 - 61.4)	51.1% (47.1 - 55.1)
Severe	0.6 (0.2 - 1.6)	0.6% (0.2 - 1.6)
Tenderness		
Any	48.2 (44.3 - 52.2)	43.6% (39.7 - 47.6)
Severe	0.6 (0.2 - 1.6)	0.6% (0.2 - 1.6)
Erythema		
Any	27.5 (24.1 - 31.2)	21.5% (18.3 - 24.9)
Severe	0.0 (0.0 - 0.6)	0.0% (0.0 - 0.6)
Swelling		
Any	25.8 (22.4 - 29.4)	21.0% (17.9 - 24.4)
Severe	0.0 (0.0 - 0.6)	0.0% (0.0 - 0.6)
DTaP-IPV//PRP~T + hepatitis B (% (95% CI)) (z=630)		
<b>Systemic reactions</b>		
Overall		
Any	60.2 (56.2 - 64.0)	
Severe	3.0 (1.8 - 4.7)	
Fever		
Any	14.6 (11.9 - 17.6)	
Severe	0.6 (0.2 - 1.6)	
Vomiting		
Any	21.7 (18.6 - 25.2)	
Severe	0.5 (0.1 - 1.4)	
Abnormal crying		
Any	37.9 (34.1 - 41.9)	
Severe	1.3 (0.5 - 2.5)	
Drowsiness		
Any	25.6 (22.2 - 29.2)	
Severe	0.5 (0.1 - 1.4)	
Appetite loss		
Any	19.0 (16.1 - 22.3)	
Severe	0.6 (0.2 - 1.6)	
Irritability		
Any	34.1 (30.4 - 38.0)	
Severe	1.0 (0.4 - 2.1)	

CI = confidence interval; z = number of doses administered with post-injection available safety data; Any = all cases, irrespective of intensity; Severe = number of participants with at least one particular symptom recorded as severe (Tenderness = child cries when injected limb is moved or the movement of the injected limb is reduced; Erythema/Swelling = longest diameter ≥5 cm; Fever = axillary temperature ≥39.0°C; Vomiting = ≥6 episodes per 24 hours or requiring parenteral hydration; Abnormal crying = more than 3 hours; drowsiness = sleeping most of the time or difficult to wake up; Appetite loss = refuses ≥3 feeds/meals or refuses most feeds/meals; Irritability = child 'inconsolable').

The pertussis antigen immunogenicity data from 36 trials of this aP formulation in combination vaccines conducted in 17 countries have also been reviewed.<sup>25</sup> In those trials, the GMTs ranged from 49 to 184 EU/ml for anti-PT and from 95 to 293 EU/ml for anti-FHA following primary immunisation. The addition of other valences, i.e. IPV and PRP~T, or concomitant administration of hepatitis B did not affect the immunogenicity of the PT and FHA antigens included in the combination.

The long-term impact of the DTaP-IPV//PRP~T combined vaccine on pertussis incidence has been surveyed in Sweden over 10 years.<sup>26,27</sup> Although the South African schedule differs from that in Sweden, we believe that these data are applicable to EPI schedules since high immunogenicity has been demonstrated in different primary vaccination regimens with this combined vaccine.<sup>25</sup> Routine primary vaccination with aP vaccines, including Pentaxim™, resulted in a marked decrease in pertussis incidence, with protection remaining high for 5 - 7 years after the third dose.<sup>28</sup>

As South Africa was close to certification as polio free at the time of the study (its last case of polio caused by a wild-type polio virus occurred in 1989<sup>29</sup>), omission of the OPV birth dose posed no risk to participants and did not pose ethical problems. Combined vaccines that include IPV are available in the South African National Immunisation Programme and the seroprotection achieved against all three poliovirus types in our study provides additional evidence for the immunogenicity of the IPV antigens included in the combination vaccine at 6, 10 and 14 weeks of age. The anti-poliovirus GMTs observed after primary vaccination were very high compared with clinical trials with this vaccine in other countries following several primary vaccination schedules.<sup>19-24</sup> The high immunogenicity of the IPV in this study is of importance because of the vaccination schedule and for maintaining population immunity against poliomyelitis following elimination of wild poliovirus circulation and cessation of OPV.<sup>30</sup> The inclusion of IPV in a DTaP combined vaccine ensures vaccination coverage as high as that for three doses of pertussis vaccine and avoids the additional vaccinations required if IPV were to be added to the schedule as a separate vaccine. Routine Hib vaccination has dramatically decreased the incidence of disease in many countries,<sup>1,3</sup> including South Africa following its introduction in 1999.<sup>31</sup> The combination of DTP antigens with PRP~T does not significantly alter the immunogenicity or efficacy of the Hib vaccine.<sup>32,33</sup> In our study the anti-PRP antibody response  $\geq 0.15$   $\mu\text{g/ml}$  in 94.6% of participants was comparable to the 98 - 98.7% rates in the Philippine and Indian studies at 6, 10 and 14 weeks.<sup>19,20</sup> The anti-PRP result is also similar to studies that used the same combined vaccine at 2, 3 and 4 months of age or 2, 4 and 6 months of age.<sup>19-24</sup> There was no negative impact when the combined vaccine and the recombinant hepatitis B vaccine were given concomitantly at separate injection sites, as the immune responses were satisfactory and safety data were acceptable for use in this South African population. The hepatitis B vaccination programme in South Africa has markedly reduced HBsAg carriage in children younger than 5 years of age.<sup>34</sup> Finally, compatibility with the EPI 6, 10 and 14 weeks of age schedule ensures the early protection of infants and avoids late administration of vaccines that might impair the success of child immunisation programmes.<sup>35,36</sup>

The DTaP-IPV//PRP~T combination and monovalent hepatitis B vaccines were well tolerated and had similar reactogenicity profiles, and their safety results reflect the good reactogenicity previously documented for aP-based combination vaccines.<sup>2,7</sup>

## Conclusion

The DTaP-IPV//PRP~T combined vaccine (Pentaxim™, an AcXim family vaccine) was highly immunogenic for all antigens when administered to infants following the 6, 10 and 14 weeks EPI schedule. The seroprotection and seroconversion rates were similar to historical data. The inclusion of IPV and PRP~T valences facilitates their addition to the national immunisation schedule with high coverage equivalent to that of three doses of DTP vaccine. The combined vaccine was compatible and well tolerated when given concomitantly with hepatitis B vaccine.

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## Assessing menopausal status in women aged 40 - 49 using depot-medroxyprogesterone acetate, norethisterone enanthate or combined oral contraception

Mags E Beksinska, Jenni A Smit, Immo Kleinschmidt, Tim M M Farley

**Background.** Determining symptoms of menopause in older users of hormonal injectable contraceptives may be challenging, owing to method-induced amenorrhoea, suppression of follicle-stimulating hormone (FSH) and vasomotor symptoms.

**Objective.** To investigate menopausal symptoms in women aged 40 - 49 using injectable contraceptives depot-medroxyprogesterone acetate (DMPA), norethisterone enanthate (NET-EN) or combined oral contraceptives (COCs), compared with non-users of hormonal contraception.

**Methods.** Women using DMPA ( $N=127$ ), NET-EN ( $N=102$ ), COCs ( $N=106$ ) and 161 non-hormonal contraceptive user controls were recruited. Baseline visit serum FSH was measured and information was collected on vasomotor symptoms and menstrual regularity.

**Results.** There was no difference in reporting of vasomotor symptoms between the groups. There was no evidence of a

difference in FSH level between non-users (mean FSH 26.7 IU/ml, SD 28.7) and DMPA users (mean FSH 23.1 IU/ml, SD 27.8) ( $p=0.64$ ). However, the NET-EN (mean FSH 11.0 IU/ml, SD 10.9) ( $p=0.003$ ) and COC groups (mean FSH 12.5 IU/ml, SD 18.7) ( $p=0.001$ ) had significantly lower FSH levels compared with the non-user group.

**Conclusion.** The lower FSH levels found in the NET-EN and COC users compared with controls may indicate a greater degree of suppression of FSH levels in these two methods, compared with DMPA. Measuring FSH levels may therefore be informative of menopausal status in DMPA users but not in NET-EN or COC users. Vasomotor symptoms may assist in assessing menopausal status in DMPA, NET-EN and COC users.

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Determining the onset of menopause in older users of hormonal injectable contraceptives depot medroxyprogesterone acetate (DMPA) and norethisterone enanthate (NET-EN) can be challenging.

Maternal, Adolescent and Child Health, Department of Obstetrics and Gynaecology, University of the Witwatersrand, Overport, Durban

Mags E Beksinska, PhD

Jenni A Smit, PhD

London School of Hygiene and Tropical Medicine, London, UK

Immo Kleinschmidt, PhD

UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, Department of Reproductive Health and Research, World Health Organization, Geneva, Switzerland

Tim M M Farley, PhD

Corresponding author: M Beksinska ([mbeksinska@match.org.za](mailto:mbeksinska@match.org.za))

These contraceptive methods may mask menopausal symptoms such as amenorrhoea, which is a common side-effect of the method itself and increases in incidence over length of time used.<sup>1</sup> DMPA has been shown to relieve vasomotor symptoms in perimenopausal women.<sup>2,3</sup> Furthermore, DMPA and NET-EN are known to suppress the mid-cycle surge of follicle-stimulating hormone (FSH) and luteinising hormone (LH), thereby reducing raised FSH levels, although the tonic release of these gonadotrophins continues at luteal phase levels.<sup>4</sup> Detection of menopause or perimenopause may, therefore, present difficulties in this group of contraceptive users. In older combined oral contraceptive (COC) users, it is recommended that FSH is measured on the seventh day of the pill-free interval.<sup>5</sup> However, appropriate advice for DMPA and NET-EN users is less clear, and it has been suggested that the options are to continue using the method until the woman reaches 55 years or to change to a non-hormonal method of contraception.<sup>6</sup>