An adolescent–adult formulation tetanus and diptheria toxoids adsorbed combined with acellular pertussis vaccine has comparable immunogenicity but less reactogenicity in children 4–6 years of age than a pediatric formulation acellular pertussis vaccine and diphtheria and tetanus toxoids adsorbed combined with inactivated poliomyelitis vaccine

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Abstract

In Canada, the fifth dose of the routine childhood immunization schedule against diphtheria, tetanus, pertussis and polio is given at 4–6 years of age. Up to 30% of children may have significant local reactions (redness, swelling) and this may be related to pertussis and diphtheria antigen content. We sought to determine if a combination product with lower content of pertussis and diphtheria toxoids (dTap) would result in fewer local reactions and not have inferior immunogenicity to a combination vaccine with higher pertussis and diphtheria content (diphtheria–tetanus–acellular pertussis–inactivated polio virus, DTaP-IPV). Healthy children aged 4–6 years with complete primary immunization series and a fourth dose of diphtheria and tetanus toxoids component pertussis inactivated polio and \textit{Haemophilus influenzae} type B conjugate vaccine were randomized to one dose of dTap, followed in 4–6 weeks by one dose of IPV or control DTaP-IPV. Immediate reactions within 30 min, solicited injection site and systemic reactions within 14 days, and unsolicited adverse events (AE) within 6 weeks post-vaccination were monitored. Serum was collected prior to immunization, and 4–6 weeks after vaccine for diphtheria, tetanus and pertussis antibodies (Ab). Sample size was designed to detect \( \geq 10\% \) difference in injection site erythema, pain or swelling between groups 593 children at eight Canadian sites completed the study; no participant withdrew because of an AE. All safety endpoints on days 0–14 were less frequent in children randomized to the dTap than DTaP-IPV group: erythema (34.6% versus 51.7%), swelling (24.2% versus 33.8%) and pain (39.6% versus 50.8%).

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versus 67.2%). Fever was also less common (8.72% versus 16.9%). All children in both study groups had seroprotective Ab levels to diphtheria and tetanus at 4–6 weeks (≥0.10 IU/mL). The majority of children in each vaccine arm had a four-fold increase in pertussis antibodies. Fever and injection site reactions are less common in 4–6 year-old-children who receive a dTap vaccine compared to DTaP-IPV, without inferior immunogenicity.

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1. Introduction

In the routine North American childhood immunization schedule, the “preschool booster” given between 4 and 6 years of age provides protection against diphtheria, tetanus, pertussis and polio. Although, the substitution of whole cell pertussis antigens with acellular pertussis antigens has resulted in reduced rates of fever, irritability and other systemic adverse events (AE) following immunization, local reactions increase in frequency with booster doses [1–3]. Up to 30% of children may have injection site redness and swelling exceeding 50 mm in diameter, although this is not associated with increased pain or reduced arm mobility in recipients of acellular pertussis-containing vaccines.

The pathophysiology underlying the phenomenon of increased frequency of injection site redness and swelling with booster doses is not clear [4,5]. It has been suggested that the pertussis and/or diphtheria antigen content may be responsible [3], or that Th2-associated or IgE-mediated immune responses [4,6] may be stimulated by priming with acellular pertussis vaccines.

We sought to determine if an adolescent/adult formulation diphtheria tetanus and acellular pertussis vaccine (dTap, Adacel™ vaccine, sanofi pasteur) followed in 4–6 weeks by one dose of injectable polio vaccine (inactivated poliomyelitis vaccine-IPVTM vaccine, sanofi pasteur) or the routine immunization diphtheria tetanus toxoids acellular pertussis polio (DTaP-IPV, Quadracel™ vaccine, sanofi pasteur) according to a computer-generated randomization list allocated in blocks. Study vaccine was administered in the deltoid by an unblinded study nurse. To maintain study masking, this nurse did not perform any study safety assessment procedures. Parents and participants were blinded to vaccine allocation.

Both vaccine formulations contain 5 μg fimbriae (FIM) types 2 and 3, 3 μg pertactin, 5 Lf tetanus toxoid, 1.5 mg aluminum phosphate (0.3 mg Al) and 0.6% 2-phenoxyethanol.

2. Methods

2.1. Participants

Healthy children ≥4 and <7 years of age, who had a documented complete primary immunization series and a fourth dose of diphtheria and tetanus toxoids component pertussis inactivated polio and Haemophilus influenzae type B conjugate vaccine (Pentacel™ vaccine) were eligible to participate. Exclusion criteria included immune disorders, chronic disease or seizure disorder, recent pertussis, receipt of immunosuppressive therapy, systemic steroids, non-steroidal anti-inflammatory drugs, investigational products or blood products, or known or suspected allergy to the study vaccines or their components.

2.2. Vaccines, randomization and immunization procedures

The study was conducted at eight centers in Canada. The protocol was reviewed and approved by the Research Ethics Board at each institution. Written informed consent was obtained from the parents or guardians of all participants before study procedures were initiated.

Children were randomized to receive one dose of adolescent/adult formulation diphtheria tetanus and acellular pertussis vaccine (dTap, Adacel™ vaccine, sanofi pasteur), followed in 4–6 weeks by one dose of injectable polio vaccine (inactivated poliomyelitis vaccine-IPV™ vaccine, sanofi pasteur) or the routine immunization diphtheria tetanus toxoids acellular pertussis polio (DTaP-IPV, Quadracel™ vaccine, sanofi pasteur) according to a computer-generated randomization list allocated in blocks. Study vaccine was administered in the deltoid by an unblinded study nurse. To maintain study masking, this nurse did not perform any study safety assessment procedures. Parents and participants were blinded to vaccine allocation.

Safety assessment was performed by study personnel blinded to vaccine allocation. Immediate reactions were observed for 30 min post-immunization. Solicited injection site events (erythema, pain, swelling, axillary node swelling, increase in arm circumference) and systemic (fever, vomiting, headache, diarrhea, nausea, chills, rash, generalized body ache, tiredness, sore and/or swollen joints) events were recorded daily for 2 weeks on a diary card by the parent or guardian. Study personnel made telephone contact with the parent/guardian on days 4 and 15 post-immunization to ask if any severe reactions (temperature ≥39.5°C), redness or swelling ≥35 mm or any reaction graded as severe or changes in the child’s health in the previous 4 days.

Unsolicited adverse events were collected up to 6 weeks post-vaccination. These included those events that elicited a
phone call to or visit with a physician, an emergency room visit or a hospitalization. Adverse events and their relatedness to the study vaccine(s) were defined and categorized according to the International Conference on Harmonization guidelines, Good Clinical Practice [6]. Moderate and severe local events were redness or swelling 10–34 and ≥35 mm, respectively. Moderate fever was predefined as ≥38.8–39.5 °C and severe fever was ≥39.5 °C. Systemic reactions were considered moderate if they interfered with daily activities but did not require medical care or absence from school or day care, and severe if they were incapacitating, the child was unable to perform usual activities, required medical care or missed school or daycare.

Blood samples were collected prior to immunization on day 0, and at a clinic visit 4–6 weeks after vaccine for diphtheria, tetanus and pertussis antibodies. Antibodies to diphtheria were measured by the ability of the test sera to protect Vero cells from a diphtheria toxin challenges and reported as IU/mL by comparison to a calibrated World Health Organization (WHO) reference serum (Lots DI-00 and DI-00/462) and were determined by the highest serum dilution that allow cell metabolism in the presence of the challenge dose. Anti-tetanus immunoglobulin G (IgG) antibodies titres were determined by an indirect ELISA method. Titres were calculated as IU/mL by comparison to control international standard (Lot TE-3), available from the WHO.

Antibodies to \textit{Bordetella pertussis} measured were anti-pertussis toxin (anti-PT), anti-filamentous haemagglutinin (anti-FHA), anti-pertactin (anti-PRN) and anti-fimbriae types 2 and 3 (anti-FIM). Using an indirect ELISA method, results were calculated in ELISA units (EU) per milliliter by comparison to a pool of in-house standard anti-sera of assigned units.

2.4. Statistical analysis

The primary hypotheses were that the anti-diphtheria and anti-tetanus toxoid antibody responses, and the injection site reactions of erythema, swelling and pain, after immunization in those receiving dTap would be non-inferior to those receiving DTaP-IPV.

The primary immunogenicity outcome was the percentages of participants achieving predefined seroprotective levels of antibody titres for tetanus and diphtheria (≥0.10 IU/mL)[7–9] in each vaccine group. The sample size was designed to detect ≥10% between-group difference in these outcomes. Diphtheria and tetanus antibody responses were considered non-inferior if the lower limit of the two-sided 90% CI for the difference in seroprotection rates between groups was ≥10%. In addition, the percentage of participants with antibody levels of ≥1.0 and ≥0.10 IU/mL were calculated for diphtheria and tetanus. Pre- and post-vaccination geometric mean titres (GMT) and four-fold rises in response rates to diphtheria, tetanus and each pertussis antigen were calculated for each study group. The primary safety outcome was the percentage of participants with injection site erythema, pain or swelling in each group; dTap was considered non-inferior to DTaP-IPV if the if the upper limit of the two-sided 90% CI was <10%.

3. Results

3.1. Participants

We enrolled 593 children in eight Canadian sites between August 2002 and January 2003. Of these, 299 children were randomized to DTaP-IPV and 294 to dTap; completion rates were high in both groups (297/299, 99.3%; 291/294, 99.0%). Mean age was 4.6 years, the age range was of 4.0–6.6 years for DTaP-IPV and 4.0–6.3 years for dTap. Fifty-two and 51% of participants were female in the respective groups and 92% were of Caucasian background.

3.2. Safety

All primary safety endpoints (erythema, swelling, pain) in the 14 days following immunization were less frequent in children randomized to dTap (Fig. 1) than DTaP-IPV. Fever was also less common (8.72% versus 16.9%).

The rates of “any” and “moderate and severe” erythema, swelling, pain and fever for days 0–3 and days 0–14 (Table 1) were compared. The non-inferiority criteria were met, that is, the upper limit of the two-sided 90% CI was <10% for all comparisons.

There was one serious adverse event, a circumcision for a pre-existing phimosis, in the dTap group. No participant withdrew because of an adverse event.

Seven participants in each group reported mild immediate injection site reactions of redness, swelling, bruising, pain, itching or erythema. All reactions resolved without intervention or sequelae, the majority within 2 days and all within 6 days of vaccination.

3.3. Immunogenicity

dTap was non-inferior to DTaP-IPV for the primary seroprotection outcomes for diphtheria and tetanus. All

Fig. 1. Percentage of adverse events rated as moderate-severe occurring days 0–14, days after immunization with dTap or DtaP-IPV as a fifth dose at 4–6 years of age.
Participants (100%) had seroprotective antibody levels (≥0.10 IU/mL) to diphtheria and tetanus at 4–6 weeks after vaccination. dTap thus met the non-inferiority criteria for this primary seroprotection outcome as the lower limit of the two-sided 90% CI was ≥10% for both diphtheria (0.0, 90% CI: 0.0–0.0) and tetanus (0.0, 90% CI: 0.0–0.0).

Levels ≥1.0 IU/mL to diphtheria and tetanus were also similar in dTap and DTaP-IPV groups: diphtheria 97.7% (95% CI, 95.1, 99.2) versus 98% (95.4, 99.4) and tetanus 100% (98.6, 100) versus 99.6% (97.8, 100). The majority of participants achieved a four-fold rise over pre-vaccination titres for both antigens (Table 2). The GMT for diphtheria was lower in the dTap compared to the DTaP-IPV group (6.10 versus 13.58); the post-vaccination tetanus GMTs were comparable.

A four-fold increase in all four pertussis antibodies was seen in the majority of children receiving dTap and DTaP-IPV (Table 2) and ranged from 87.6 to 96.8%. GMTs were higher to PRN and FIM in the dTap group, and lower to PT and FHA than the DTaP-IPV group (Table 2).

### 4. Discussion

We have shown that reduction of pertussis and diphtheria antigen content in the childhood booster at 4–6 years results in reduced frequency of erythema, swelling, pain and fever without inferior immunogenicity. This suggests that booster vaccines formulated for adolescents and adults, with reduced content of diphtheria toxoid and the pertussis antigens FHA and PT, could be successfully used to boost the immune responses of preschool children. Although injection site reactions are well-tolerated, resolve within 14 days [5] and may not affect parental acceptance of vaccines [10], any measure to increase vaccine safety is likely to be welcomed by regulators, manufacturers, the medical community, and parents. Furthermore, the prospect of introducing additional acellular pertussis–diphtheria–tetanus vaccines in adolescence and adulthood [11,12] warrants continued vigilance for increased frequency of local reactions with booster doses.

In Canada, the adolescent/adult formulation dTap vaccine can be used for primary immunization of children 7 years of age and older [12].

### Table 1
Summary of primary safety endpoints in 593 children randomized to one dose of dTap, followed in 4–6 weeks by one dose of IPV or control DTaP-IPV

<table>
<thead>
<tr>
<th>Any reaction</th>
<th>DTaP (%)</th>
<th>DTaP-IPV (%)</th>
<th>Difference (90% CIa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0–3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>34.23</td>
<td>51.03</td>
<td>−16.81 (−23.42, −10.19)</td>
</tr>
<tr>
<td>Swelling</td>
<td>23.83</td>
<td>33.79</td>
<td>−9.97 (−16.08, −3.86)</td>
</tr>
<tr>
<td>Pain</td>
<td>38.26</td>
<td>67.24</td>
<td>−27.64 (−35.47, −22.51)</td>
</tr>
<tr>
<td>Fever</td>
<td>2.68</td>
<td>7.93</td>
<td>−5.25 (−8.28, −2.22)</td>
</tr>
<tr>
<td>Days 0–14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>34.56</td>
<td>51.72</td>
<td>−17.16 (−23.78, −10.54)</td>
</tr>
<tr>
<td>Swelling</td>
<td>24.16</td>
<td>33.79</td>
<td>−9.63 (−15.76, −3.51)</td>
</tr>
<tr>
<td>Pain</td>
<td>39.60</td>
<td>67.24</td>
<td>−27.64 (−34.15, −21.14)</td>
</tr>
<tr>
<td>Fever</td>
<td>8.72</td>
<td>16.90</td>
<td>−8.17 (−12.68, −3.66)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate–severe reaction</th>
<th>DTaP (%)</th>
<th>DTaP-IPV (%)</th>
<th>Difference (90% CIa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>2.68</td>
<td>7.93</td>
<td>−5.25 (−8.28, −2.22)</td>
</tr>
</tbody>
</table>

a 90% CI, lower and upper limits of the two-sided 95% confidence interval for the difference.

### Table 2
Summary of post-vaccination four-fold response rates and geometric mean titres at 4–6 weeks in 593 children randomized to one dose of dTap, followed in 4–6 weeks by one dose of IPV, or control DTaP-IPV

<table>
<thead>
<tr>
<th>dTap</th>
<th>% (n)</th>
<th>LCL</th>
<th>UCL</th>
<th>DTaP-IPV</th>
<th>% (n)</th>
<th>LCL</th>
<th>UCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Four-fold response rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphtheria</td>
<td>89.8 (238)</td>
<td>85.5</td>
<td>93.2</td>
<td>93.7 (236)</td>
<td>89.9</td>
<td>96.3</td>
<td></td>
</tr>
<tr>
<td>Tetanus</td>
<td>94.3 (250)</td>
<td>90.8</td>
<td>96.8</td>
<td>93.7 (236)</td>
<td>89.9</td>
<td>96.3</td>
<td></td>
</tr>
<tr>
<td>PT</td>
<td>91.9 (239)</td>
<td>87.8</td>
<td>94.9</td>
<td>96.8 (243)</td>
<td>93.8</td>
<td>98.6</td>
<td></td>
</tr>
<tr>
<td>FHA</td>
<td>88.1 (230)</td>
<td>83.6</td>
<td>91.8</td>
<td>92.8 (233)</td>
<td>88.9</td>
<td>95.7</td>
<td></td>
</tr>
<tr>
<td>FIM</td>
<td>94.6 (247)</td>
<td>91.2</td>
<td>97.0</td>
<td>87.6 (220)</td>
<td>82.9</td>
<td>91.5</td>
<td></td>
</tr>
<tr>
<td>PRN</td>
<td>94.3 (246)</td>
<td>90.7</td>
<td>96.7</td>
<td>92.0 (231)</td>
<td>88.0</td>
<td>95.1</td>
<td></td>
</tr>
<tr>
<td>GMTs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphtheria</td>
<td>6.10</td>
<td>5.42</td>
<td>6.86</td>
<td>13.58</td>
<td>11.50</td>
<td>16.04</td>
<td></td>
</tr>
<tr>
<td>Tetanus</td>
<td>7.20</td>
<td>6.67</td>
<td>7.77</td>
<td>6.65</td>
<td>6.10</td>
<td>7.25</td>
<td></td>
</tr>
<tr>
<td>PT</td>
<td>297.14</td>
<td>269.32</td>
<td>327.83</td>
<td>331.33</td>
<td>298.98</td>
<td>367.17</td>
<td></td>
</tr>
<tr>
<td>FHA</td>
<td>198.04</td>
<td>179.57</td>
<td>218.41</td>
<td>258.14</td>
<td>235.48</td>
<td>282.99</td>
<td></td>
</tr>
<tr>
<td>FIM</td>
<td>1177.19</td>
<td>1048.75</td>
<td>1321.36</td>
<td>737.62</td>
<td>658.56</td>
<td>826.16</td>
<td></td>
</tr>
<tr>
<td>PRN</td>
<td>303.76</td>
<td>270.53</td>
<td>341.08</td>
<td>243.12</td>
<td>214.90</td>
<td>275.05</td>
<td></td>
</tr>
</tbody>
</table>

GMT, geometric mean titre 4–6 weeks after vaccination; LCL and UCL, upper and lower confidence limits of the two-sided 95% exact confidence interval for the proportion; PT, pertussis toxin; FHA, filamentous haemagglutinin; FIM, fimbrae types 2 and 3; PRN, pertactin.
age or older who are not immunized in early infancy [13,14].
In future, it is reasonable to consider that dTap could be used
for the booster dose in children 4–6 years of age in order
to reduce injection site events. In this country, this would mean
that the child would receive an extra immunization since the
National Advisory Committee on Immunization recommends a dose of IPV be included in the 4–6 year booster dose.
A dTap-IPV formulation has been studied and is available
for use in children 3 years of age or older in some European
countries [15].

The rates of local and systemic events observed in the
DTaP-IPV group in this study are similar to those reported
from previous published studies. In a previous Canadian
study of DTaP-IPV, 35% of parents recalled any redness and
22% recalled any swelling when surveyed after booster vac-
cination [10]. In 205 children receiving DTaP-IPV booster
at 4–6 years of age, research personnel identified redness
≥ 20 mm in 37.6% of children and ≥ 50 mm in 24.4% of chil-
dren, swelling ≥ 20 mm in 50.2% and ≥ 50 mm in 20.5% and
tenderness in less than 5% on day 3 post-injection [5]. Ren-
nels et al. reported that of 121 children receiving the fifth
dose of a variety of pediatric formulation dTap vaccines,
8.3–27.3% had swelling ≥ 50 mm [1]. By contrast, lower rates
of reactions have been reported when the acellular pertussis-
containing childhood series is followed by the dTap. In an
open-label study of dTap, no fever, unsolicited symptoms or
injection site events that prevented normal activities or were
> 50 mm diameter were reported in 6–8 year-old-children
receiving dTap [16]. In a randomized controlled trial, compar-
ing DTaP-IPV to dTap children receiving the adolescent/adult
formulation vaccine also had fewer symptoms (pain in 20%
and limited arm motion in 14%) [15]. It is reasonable to con-
clude then that the adolescent/adult formulation vaccine is
less reactogenic when given as the fifth dose than vaccines
with higher diphtheria and pertussis content that are currently
part of the childhood schedule.

The immunogenicity of both vaccines evaluated was con-
sistent with clinical protection in the majority of subjects.
Not unexpectedly we observed a lower GMT for diphtheria
in the dTap group; the clinical significance of this finding
is unknown. Immunogenicity levels accepted as correlating
with protection against diphtheria and tetanus (≥ 0.10 IU/mL)
were achieved in by all participants and levels associated with
long term protection (≥ 1.0 IU/mL) were achieved in most par-
ticipants (≥ 97%). Duration of protection cannot be inferred
from these data. Since the next booster dose for diphtheria
would be in 10 years, the possibility that reduced GMTs
might require a shorter booster interval should be explored.
Duration of protection is generally unknown at the time any
vaccine is approved for routine use and should be followed
with surveillance programs.

Although the frequency of injection site inflammation
was reduced in children receiving reduced content pertussis and
diphtheria vaccines, these were common. Other explanations
for these events should be explored including the type of
adjuvant or preservative and injection technique.

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