ADVERSE EVENTS POST-DTAP AND DTwP VACCINATION IN THAI CHILDREN

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Abstract. We conducted a prospective study to compare the development of fever (axillary T≥37.9°C) within 4 hours of vaccination, determine the proportion of children who develop high fever (T≥39°C) and evaluate parental days missed from work due to their children’s vaccination with either the diphtheria-tetanus-whole cell pertussis (DTwP) or diphtheria-tetanus-acellular pertussis (DTaP) vaccine. The results of this study can help physicians and parents decide whether to have their child vaccinated with the DTwP or more expensive DTaP vaccine. We studied 140 healthy Thai children aged 2 months to 6 years from December 2011 to March 2012 who presented for vaccination. Parents recorded their child’s temperature, local and systemic adverse reactions and missed days from work due to these adverse events on a diary card. Of the 140 participants, 72 received the DTwP vaccine and 68 received the DTaP vaccine. The median (IQR) age was 4 (2-6) months and the median weight was 7.1 (5.6-8.7) kg. Twenty children developed fever (axillary T≥37.9°C) within 4 hours following vaccination, 17 (23.6%) had received the DTwP vaccine and 3 (4.4%) had received the DTaP vaccine (p=0.040). One child (1.4%) who had received the DTwP vaccine and none who received the DTaP vaccine developed high fever (T≥39°C) within 4 hours of vaccination (p=0.329). Parents of two children who received the DTwP vaccine and one child who received the DTaP vaccine missed work following vaccination (p=0.059). In conclusion, children who received the DTwP vaccines were more likely to have early post-vaccination fever and higher fever but there was no significant difference between the two groups in parental days lost from work.

Keywords: adverse events, fever, DTwP, DTaP, whole-cell pertussis vaccine, acellular pertussis vaccine, Thailand

INTRODUCTION

Diphtheria, pertussis and tetanus (DPT) are important vaccine-preventable diseases. Most countries include vaccines against these diseases in their national immunization programs (Guiso et al, 2011; Edwards and Decker, 2013). Most developing countries use whole-cell pert-
tussis (wP) based vaccines since they are more affordable than acellular pertussis (aP) based vaccines (WHO, 2013a). Studies from the US and Europe have shown post-vaccination fever is more common with DTwP vaccines than with diphtheria-tetanus (DT) and DTaP vaccines (Waigh et al, 1983; Ipp et al, 1987; Blumberg et al, 1991; Afari et al, 1996; Gustafsson et al, 1996; Jefferson et al, 2003). Studies among Thai children have also found that aP vaccines are less reactogenic than wP vaccines (Lolekha et al, 2001; Thisyakorn et al, 2009; 2010; Kosalaraksa et al, 2011). Febrile seizures rarely occur and have been linked to pertussis antigens (Principi and Esposito, 2013). The use of the wP vaccine was temporarily suspended in Vietnam because of serious adverse events reported among young infants (WHO, 2013b).

Among vaccine-related adverse events, fever is an important source of parental anxiety (Sullivan and Farrar, 2011) and concern for clinicians. It may occur early post-vaccination. To our knowledge, there have been no published studies from Asia regarding fever within 4 hours post-vaccination comparing wP and aP vaccines.

The objectives of our study were: to compare the development of fever (axillary T≥37.9°C) within 4 hours of vaccination; determine the proportion of children who develop high fever (T≥39°C); and evaluate parental days missed from work due to their children’s vaccination with either the DTwP or DTaP vaccine. The results of this study can inform physicians and parents in trying to decide which vaccine to chose for the child.

MATERIALS AND METHODS

Study design

We conducted a prospective, observational study from December 2011 to January 2012 among 150 infants and children attending the well baby clinic of Phramongkutklao Hospital in Bangkok, Thailand for DTP vaccination. The doctor obtained a medical history, reviewed the vaccination record, performed a physical examination and explained the difference between the two types of vaccines to the parents who chose either the DTwP or the DTaP vaccine for their child.

The parents or legal guardians were invited to participate in the study following the child’s vaccination. Written informed consent was obtained from the parents prior to participation in the study. The parents were requested to keep a diary of the child’s axillary temperature (T) at 4, 24, 48 and 72 hours post-vaccination, as well as record other local or systemic adverse events, such as fussiness, crying, lost sleep by parents or child, missed days from work by the parents due to adverse events, the use of antipyretics/analgesics and any medical consultations within 72 hours of vaccination. The diaries were returned by mail. For parents who were unable to return the diary, the data were collected by telephone interview. No acetaminophen (paracetamol) prophylaxis was recommended. However, parents were advised to give acetaminophen (paracetamol) (10 mg/kg/dose) every 4 hours for a T≥37.9°C until fever defervescence.

Ethical approval

This study was approved by the Ethics Review Committees of the Faculty of Tropical Medicine, Mahidol University (MUTM 2011-065-01) and the Institutional Review Board of the Royal Thai Army Medical Department in Bangkok, Thailand.

Study participants

Healthy Thai children aged 2 months to 6 years were included in the study.
Those with a fever on the day of enrollment, a history of heart, lung, kidney or central nervous system disorders (including seizures), immunodeficiency or allergy to any vaccine components were excluded from the study.

Study vaccines

For the DTaP-based vaccines, one of the following vaccines was administered intramuscularly: 1) combined diphtheria-tetanus-acellular pertussis, inactivated polio vaccine (Infanrix® IPV) lot number AC 20B190DB (GlaxoSmithKline, Wavre, Belgium); 2) combined diphtheria-tetanus-acellular pertussis, inactivated polio, hepatitis B and Haemophilus influenzae type b vaccine (Infanrix® hexa) lot number A21CB132B (GlaxoSmithKline, Wavre, Belgium); 3) combined diphtheria-tetanus-acellular pertussis, inactivated polio and Haemophilus influenzae type b vaccine (Infanrix®-IPV/Hib) lot number AC 20CA656C (GlaxoSmithKline, Wavre, Belgium); and 4) combined diphtheria-tetanus-acellular pertussis, inactivated polio and Haemophilus influenzae type b vaccine (Pentaxim®) lot number G2216-1 (Sanofi Pasteur, Lyon, France).

For the DTwP-based vaccines, one of the following vaccines was administered intramuscularly: 1) combined diphtheria-tetanus-whole cell pertussis vaccine [(DTwP (India)] lot number 027P0015A (Serum Institute of India, Pune, India); 2) combined diphtheria-tetanus-whole cell pertussis and hepatitis B vaccine (DTwP+HBV) lot number 03021001A (Serum Institute of India, Pune, India); and 3) combined diphtheria-tetanus-whole cell pertussis, hepatitis B and Haemophilus influenzae type b vaccine (Quinvaxem®) lot number 0451386 (Novartis, Seoul, Korea).

Adverse event assessment

An adverse event (AE) was defined as any untoward medical occurrence in a subject administered a vaccine, which did not necessarily include a causal relationship with the vaccine (European Medicines Agency, 1995).

A serious adverse event (SAE) was defined as any undesirable experience associated with the vaccine resulting in death, hospitalization, disability, permanent damage or other serious medical event, such as seizures/convulsions, that may or may not have resulted in hospitalization, or was life threatening (US Food and Drug Administration, 2013).

Fever was considered low grade if the axillary temperature was 37.9ºC to 38.4ºC, moderate if 38.5ºC to 38.9ºC, high if 39ºC to 40ºC and very high if >40ºC. Pain at the injection site was categorized as mild if there was no interference with activity, moderate if an analgesic (non-narcotic) was needed to be given for >24 hours, or if symptoms interfered with activity, severe if there was the need to use a narcotic pain reliever, or if daily activity was prevented and serious if there was an emergency room visit or hospitalization (US Food and Drug Administration, 2007).

Sample size calculation

The sample size was calculated using Epi Info version 3.5.3 based on prior data that fever developed in 9.8% (Afari et al, 1996) and 31.5% of children (Cody et al, 1981) who received the DTaP or DTwP vaccines, respectively. Sixty-two subjects were required to reject the null hypothesis that the proportion of fever in the two groups was equal with an 80% power and a confidence level of 95%. The total sample size was determined to be 75 subjects per group for an estimated dropout rate of 20%.

Data analysis

Data analysis included all partici-
Study participants

A total of 150 children were enrolled in the study, of which 75 received a DTaP-based vaccine and 75 received a DTwP-based vaccine. Of 150 enrolled participants, 140 (93.3%) were included in the analysis (68 and 72 in the DTaP and DTwP-based vaccine groups, respectively) (Fig 1). Ten children were lost to follow-up, 7 from the DTaP-based vaccine group and 3 from the DTwP-based vaccine group.

Seventy-seven study participants (55%) were male and 110 (78.6%) were aged <6 months. The median age was 4 months (IQR 2-6). The demographic characteristics of the study participants are summarized in Table 1. There were no statistically significant differences between the two groups in regard to median age, gender or median weight ($p$>0.05).

Of the 68 children who received DTaP-based vaccines, 36 (52.9%), 20 (29.4%), 10 (14.7%) and 2 (2.9%) received the Infanrix™ hexa, Infanrix™ IPV/Hib, Infanrix™ IPV, and Pentaxim® vaccines, respectively.

Of the 72 children who received DTwP-based vaccines, 38 (52.8%), 28 (38.9%) and 6 (8.3%) received the DTwP, DTwP+HBV and Quinvaxem® vaccines, respectively.

Local adverse reactions

Local adverse reactions were pain and swelling at the injection site (Fig 2). Swelling at the injection site was the most common local reaction seen in the DTwP group (40/72, 55.5%). It was mild
Table 1
Demographic characteristics of children who received the DTaP and DTwP-based vaccines.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>DTaP-based vaccine (n=68)</th>
<th>DTwP-based vaccine (n=72)</th>
<th>Total (N=140)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>37 (54.4)</td>
<td>40 (55.6)</td>
<td>77 (55)</td>
</tr>
<tr>
<td>Female</td>
<td>31 (45.6)</td>
<td>32 (44.4)</td>
<td>63 (45)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6 months</td>
<td>57 (83.8)</td>
<td>53 (73.6)</td>
<td>110 (78.6)</td>
</tr>
<tr>
<td>7-18 months</td>
<td>11 (16.2)</td>
<td>8 (11.1)</td>
<td>19 (13.6)</td>
</tr>
<tr>
<td>19-36 months</td>
<td>0 (0)</td>
<td>2 (2.8)</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>37-48 months</td>
<td>0 (0)</td>
<td>8 (11.1)</td>
<td>8 (5.7)</td>
</tr>
<tr>
<td>&gt;48 months</td>
<td>0 (0)</td>
<td>1 (1.4)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Median age (IQR) in months</td>
<td>4 (2-6)</td>
<td>4.3 (2-18)</td>
<td>4 (2-6)</td>
</tr>
<tr>
<td>Median weight (IQR) in kilograms</td>
<td>7 (5.7-8.2)</td>
<td>7.1 (5.6-9.5)</td>
<td>7.1 (5.6-8.7)</td>
</tr>
</tbody>
</table>

Table 2
Incidence by time of fever in children who received DTaP and DTwP-based vaccines.

<table>
<thead>
<tr>
<th>Onset</th>
<th>DTaP</th>
<th>Total</th>
<th>DTwP</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>37.9-38.5-39-41°C</td>
<td></td>
<td>37.9-38.5-39-41°C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 4 hours</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>4-48 hours</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>49-72 hours</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total fever prevalence</td>
<td>9</td>
<td>4</td>
<td>2</td>
<td>15</td>
<td>33</td>
</tr>
</tbody>
</table>

in severity and the onset was 4 to 6 hours after injection. The duration of swelling was 2 to 7 days. Swelling was significantly more common in the DTwP group than the DTaP group (p<0.001).

Systemic adverse reactions

Fever. Of the 68 children in the DTaP group, 15 (22%) developed fever (T≥37.9°C) from 4 to 72 hours after vaccination (Fig 2). Of the 72 children who received the DTwP vaccine, 33/72 (45.8%) had fever during the same time period (p=0.078) (Table 2).

Twenty children developed fever (T≥37.9°C) within 4 hours of having the vaccine. Of these, 17 (23.6%) received the DTwP vaccine and 3 (4.4%) received the DTaP vaccine (p=0.040) (Table 2). High fever (T≥39°C) within 4 hours of the vaccine was reported in one child who received the DTwP vaccine and none among those who received the DTaP vaccine (p=0.329) (data not shown).

Among the DTwP-based vaccines, children who received the DTwP vaccine had a significantly greater incidence of fever than children who received the DTwP+HBV and Quinvaxem vaccines.
One infant who had the DTaP vaccine cried for 4 hours. He also had swelling at the injection site following vaccination.

Lost sleep. Children in the DTwP group did not lose any more sleep than the DTaP group ($p=0.226$) (Fig 2, Table 3).

Serious adverse events

No serious adverse events were observed in this study.

Effect on parents

The parents of the children in the DTwP group did not lose any more sleep than the parents of the children in the DTaP group ($p=0.328$). Two parents of children in the DTwP group and 1 parent of a child in the DTaP group did not return to work because they had to care for a febrile child ($p=0.059$).

Medical consultation

Parents of 3 children who had the DTwP and 3 children who had the DTaP vaccine consulted a physician within 72 hours of having the vaccine ($p=0.94$).

DISCUSSION

Our findings show the whole-cell pertussis vaccines caused more local and systemic adverse reactions than the acellular pertussis vaccines among Thai children. Swelling at the injection site was noted in 55.5% of children who received the whole-cell pertussis vaccine and 7.4% in those who received the acellular pertussis vaccine. These findings are consistent with a study from southern Ghana (Afari...
Table 3
Comparison of signs and symptoms among children who received DTaP and DTwP-based vaccines.

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>DTaP (N=68)</th>
<th>DTwP (N=72)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37.9°C-38.3°C</td>
<td>9 (13.2)</td>
<td>24 (33.3)</td>
<td>0.022</td>
</tr>
<tr>
<td>38.4°C-38.9°C</td>
<td>4 (5.9)</td>
<td>5 (6.9)</td>
<td></td>
</tr>
<tr>
<td>T ≥ 39°C</td>
<td>2 (2.9)</td>
<td>4 (5.5)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>53 (77.9)</td>
<td>39 (54.2)</td>
<td></td>
</tr>
<tr>
<td>Fussiness</td>
<td>16 (23.5)</td>
<td>30 (47.6)*</td>
<td>0.007</td>
</tr>
<tr>
<td>Duration of crying</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.5 hour</td>
<td>12 (17.6)</td>
<td>15 (20.8)</td>
<td>0.052</td>
</tr>
<tr>
<td>0.5-1 hour</td>
<td>2 (2.9)</td>
<td>12 (16.7)</td>
<td></td>
</tr>
<tr>
<td>2-3 hours</td>
<td>3 (4.4)</td>
<td>1 (1.4)</td>
<td></td>
</tr>
<tr>
<td>&gt;3 hours</td>
<td>1 (1.5)</td>
<td>2 (2.8)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>50 (73.5)</td>
<td>42 (58.3)</td>
<td></td>
</tr>
<tr>
<td>Amount of lost sleep</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 hour</td>
<td>2 (2.9)</td>
<td>6 (8.3)</td>
<td>0.226</td>
</tr>
<tr>
<td>1-3 hours</td>
<td>9 (13.2)</td>
<td>12 (16.7)</td>
<td></td>
</tr>
<tr>
<td>4-6 hours</td>
<td>1 (1.5)</td>
<td>1 (1.4)</td>
<td></td>
</tr>
<tr>
<td>&gt;6 hours</td>
<td>0 (0)</td>
<td>3 (4.2)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>56 (82.4)</td>
<td>50 (69.4)</td>
<td></td>
</tr>
<tr>
<td>Medical consultation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (4.4)</td>
<td>3 (4.2)</td>
<td>0.94</td>
</tr>
<tr>
<td>No</td>
<td>65 (95.6)</td>
<td>69 (95.8)</td>
<td></td>
</tr>
</tbody>
</table>

*aNine children who received the DTwP vaccine were not considered for the analysis of fussiness because they were aged >46 months (N=63).

et al, 1996) where 31% (122/394) of the children who received the whole-cell vaccine had injection site swelling compared to 2% (8/399) of the children who received the acellular vaccine. Previous studies among infants from Thailand and Singapore found the acellular pertussis vaccines to be safe and less reactogenic (Lolekha et al, 2001; Thisyakorn et al, 2009, 2010; Kosalaraksa et al, 2011; Lim et al, 2011). A study from the US found the acellular pertussis vaccine was not associated with serious adverse events among children aged 4-6 years (Daley et al, 2014).

In our study, the DTaP vaccine group was associated with a lower incidence of post-vaccination fever than the DTwP vaccine. This finding is similar to previous studies by Bernstein et al (1993) and Afari et al (1996). The incidence of post-DTwP vaccine fever among children in our study was 23.6%. A previous study found the incidence of post-DTwP vaccine fever of 15% (Waight et al, 1983). Studies by Cody
et al (1981), Long et al (1990) and Bernstein et al (1993) found higher incidences of post-DTwP vaccine fever of 31.5%, 42% and 90%, respectively. The incidence of post-DTaP vaccine fever among children in our study was 4.4%. A previous study found the incidences of post-DTaP fever to be 7.27%-9.8% (Afari et al, 1996) but another found the incidence to be 52.0% (Bernstein et al, 1993). The differences in adverse reaction rates may be due to differences in DTwP vaccine preparations, production lots, children’s ages, dose series, study methods and time period for measuring the temperature (Long et al, 1990). The various DTaP vaccines may have had different vaccine preparations and quantities of antigen (Decker et al, 1995).

The whole-cell pertussis vaccine is a suspension of killed Bordetella pertussis organisms (Edwards et al, 2013). It is one of the most reactogenic vaccines (Edwards and Decker, 2013), possibly due to residual levels of active pertussis toxin and endotoxin (WHO, 2007). Baraff et al (1989) found a significant association \( (p=0.004) \) between fever in children and the endotoxin level in the DTwP vaccine. In one study (Baraff et al, 1989), children who received the whole-cell vaccine with an endotoxin level of \( \leq 2,500 \) EU had a lower frequency of fever (20.6%) than those who received the whole-cell vaccine with an endotoxin level of 40,000 EU (55.1%).

The use of acetaminophen as prophylaxis for fever following vaccination with the DTwP vaccine has occasionally been recommended by clinicians (Dhingra and Mishra, 2011). Ipp et al (1987) found this can significantly reduce fever; they found fever \( (T>38^\circ C) \) developed in 26.6% of infants who received prophylactic acetaminophen compared to 43.5% of infants who did not \( (p<0.0005) \). The use of acetaminophen in our study could have confounded the incidence of fever; however, it is unlikely to have confounded the difference in incidence between the DTaP and DTwP groups, since the proportions of children who received prophylactic acetaminophen in our study were not significantly different.

Fussiness was more common among infants who received DTwP-based vaccines. This finding is consistent with other studies (Bernstein et al, 1993; Greco et al, 1996). A meta-analysis of the effect of pertussis vaccines among children (Jefferson et al, 2003) found a significant association between crying for \( >2 \) hours and local injection site reactions, such as swelling and induration, among those given DTwP vaccines. Two subjects in our study had swelling at the injection site within 4 hours of vaccination. None of the children in our study had high-pitched crying.

Serious adverse reactions, such as convulsions, infantile spasms, hypotonic-hyporesponsive episodes or encephalopathy, were not observed in this study. A larger sample size might be required to detect these events.

In Germany, a study comparing indirect non-medical costs, such as parental work loss due to adverse events associated with pertussis vaccines, found acellular pertussis vaccines might be more cost-effective than whole-cell vaccines (Tormans et al, 1998). A cost-benefit analysis of the use of either DTaP or DTwP vaccines among 4.1 million American children found that despite the extra cost of the acellular pertussis vaccine, there was greater acceptance of the vaccine due to fewer adverse events (Ekwueme et al, 2000).

Although DTwP-based vaccines were associated with more common adverse events, most of the adverse events seen
in our study were mild and tolerable. Our study results show DTwP-based vaccines may still be recommended for use in Thai children. The WHO, in a position paper on pertussis vaccines, noted that there is no need to switch from whole cell pertussis-based vaccines to acellular pertussis containing vaccines, since there is no proven major benefit from such a change (WHO, 2014).

Our study had a number of limitations including: 1) selection bias because there was no randomization; 2) observational bias because the children’s parents or guardians knew the kind of vaccine being given. In addition, they might perceive some adverse events as “acceptable” and therefore did not report them to the study investigator. To minimize this limitation, a standardized questionnaire was used and parents/guardians were trained on how to use the study diary; 3) recall bias among parents who did not record in the diary but gave the data by telephone interview; and 4) the use of acetaminophen as prophylaxis for fever might have had a confounding effect on the incidence of fever and other adverse events in our study.

In our study, children who received DTwP-based vaccines were significantly more likely to have fever within 4 hours post-vaccination, but not parental days missed from work, than children who received the DTaP-based vaccines. The mild nature of the adverse events leads us to conclude DTwP-based vaccines can still be used in Thai children.

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