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≥37.9ºC) within 4 hours of vaccination, determine the proportion of children who develop high fever (T≥39ºC) 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≥39ºC) 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

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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 per-

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 (Waight *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≥37.9ºC) within 4 hours of vaccination; determine the proportion of children who develop high fever (T≥39ºC); 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≥37.9ºC 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-

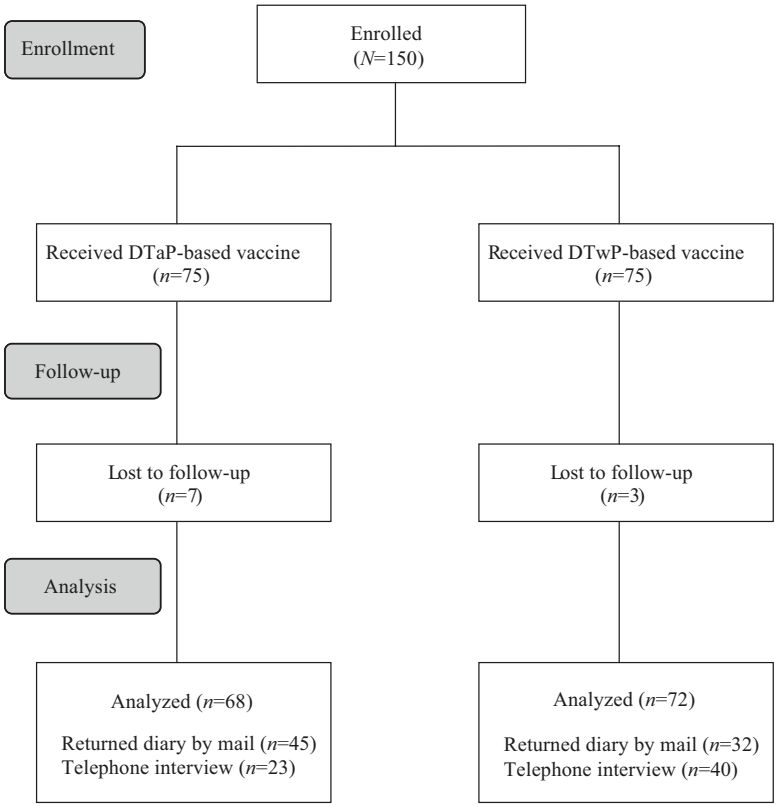

Fig 1–Study subjects.

pants with complete data. Descriptive statistics included percentages for categorical variables and median and interquartile ranges for continuous variables. The chi-square test (χ^2) or Fisher's exact test were used where appropriate for categorical variables. Statistical analyses were conducted using SPSS, version 18.0 (IBM, Amonk, NY). A p-value <0.05 was considered statistically significant.

RESULTS

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.

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

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

Onset	DTaP			Total	DTwP			Total	*p*-value
	37.9-38.4ºC	38.5-38.9ºC	39-41ºC		37.9-38.4ºC	38.5-38.9ºC	39-41ºC		
Within 4 hours	3	0	0	3	14	2	1	17	0.040
4-48 hours	6	4	2	12	10	3	2	15	0.025
49-72 hours	0	0	0	0	0	0	1	1	0.496
Total fever prevalence	9	4	2	15	24	5	4	33	0.078

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≥37.9ºC) 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≥37.9ºC) 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≥39ºC) 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

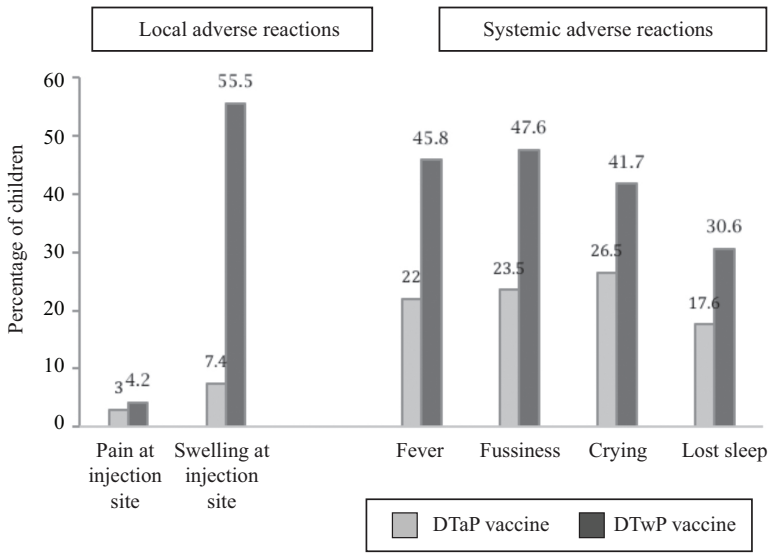

Fig 2–Local and systemic adverse reactions with the DTaP and DTwP vaccines.

(23/38 (60.5%) *vs* 9/28 (32.1%) and 1/6 (16.7%), respectively; p=0.024).

Acetaminophen was given to prevent fever in 25% (18/72) and 19.1% (13/68) of DTwP and DTaP vaccine recipients, respectively.

Fussiness. Children who received DTwP-based vaccines had a significantly greater incidence of fussiness than DTaP-based vaccine recipients (p=0.007). The parents of 30 children in the DTwP group (47.6%) and 16 in the DTaP group (23.5%) reported fussiness described as either refusal to play or clearly played less than usual (Table 3).

Crying. Children in the DTwP group cried slightly more often (p=0.052) than those in the DTaP group, with durations varying from less than 30 minutes to greater than 3 hours (Fig 2, Table 3). Of those who cried for more than 3 hours, two infants who had the DTwP vaccine cried for 4 hours and one for 7 hours. Both had swelling at the injection site following vaccination. 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.

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

[a]Nine 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 ≤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>38ºC) 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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REFERENCES

Afari EA, Kamiya Y, Nkrumah FK, *et al*. Randomized controlled trial of acellular diphtheria, tetanus vaccines in Southern Ghana. *Ann Trop Pediatr* 1996; 16: 39-48.

Baraff LJ, Manclark CR, Cherry JD, Christenson P, Marcy SM. Analyses of adverse reactions to diphtheria and tetanus toxoids pertussis and vaccine by vaccine lot, endotoxin content, pertussis vaccine potency and percentage of mouse weight gain. *Pediatr Infect Dis J* 1989; 8: 502-7.

Bernstein DI, Smith VE, Schiff GM, Rathfon HM, Boscia JA. Comparison of acellular pertussis vaccine with whole cell vaccine as a booster in children 15 to 18 months and 4 to 6 years of age. *Pediatr Infect Dis J* 1993; 12: 131-5.

Blumberg DA, Mink CM, Cherry JD, *et al*. Comparison of acellular and whole-cell pertussis-component diphtheria-tetanus-pertussis vaccines in infants. The APDT Vaccine Study Group. *J Pediatr* 1991; 119: 194-204.

Cody C, Baraff LJ, Cherry JD, *et al*. Nature and rates of adverse reactions associated with DT and DT immunizations in infants and children. *Pediatrics* 1981; 68: 650-60.

Daley MF, Yih WK, Glanz JM, *et al*. Safety of diphtheria, tetanus, acellular pertussis and inactivated poliovirus (DTaP-IPV) vaccine. *Vaccine* 2014; 32: 3019-24.

Decker MD, Edwards KM, Steinhoff MC, *et al*. Comparison of 13 acellular pertussis vaccines: adverse reactions. *Pediatrics* 1995; 96: 557-66.

Dhingra B, Mishra D. Immediate versus as-needed acetaminophen for post-immunisation pyrexia. *Ann Trop Paediatr* 2011; 31: 339-44.

Edwards KM, Decker MD. Pertussis vaccines. In: Plotkin SA, Orenstein WA, Offit PA, eds. Vaccines. 6th ed. Edinburg: Elsevier/ Saunders, 2013: 447-92.

Ekwueme DU, Strebel PM, Hadler SC, Meltzer MI, Allen JW, Livengood JR. Economic evaluation of use of diphtheria, tetanus, and acellular pertussis vaccine or diphtheria, tetanus, and whole-cell pertussis vaccine in the United States, 1997. *Arch Pediatr Adolesc Med* 2000; 154: 797-803.

European Medicines Agency. ICH Topic E2A. Clinical safety data management: definitions and standards for expedited reporting. June 1995 CPMP/ICH/377/95. London: EMEA, 1995. [Cited 2013 Dec 8]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002749.pdf

Greco D, Salmaso S, Mastrantonio P, *et al*. A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. *N Engl J Med* 1996; 334: 341- 8.

Guiso N, Liese J, Plotkin S. The Global Pertussis Initiative: Meeting report from the fourth regional roundtable meeting, France, April 14-15, 2010. *Hum Vaccines* 2011; 7: 481-8.

Gustafsson L, Hallander HO, Olin P, Reizenstein E, Storsaeter, J. A controlled trial of a two-component acellular, a five component acellular, and a whole-cell pertussis vaccine. *N Engl J Med* 1996; 334: 349-55.

Ipp MM, Gold R, Greenberg S, *et al*. Acetaminophen prophylaxis of adverse reactions following vaccination of infants with diphtheria-pertussis tetanus toxoids-polio vaccine. *Pediatr Infect Dis J* 1987; 6: 721-5.

Jefferson T, Rudin M, DiPietrantonj C. Systematic review of the effects of pertussis vaccines in children. *Vaccine* 2003 May 16; 21 (17-18): 2003-14.

Kosalaraksa P, Thisyakorn U, Benjaponpitak S, Chokephaibulkit K, Santos-Lima E. Immunogenicity and safety study of a new DTaP-IPV-Hep B-PRP-T combined vaccine compared to a licensed DTaP-IPV-Hep B// PRP-T comparator, both concomitantly administered with 7-valent pneumococcal conjugate vaccine at 2, 4, and 6 months of age in Thai infants. *Int J Infect Dis* 2011; 15: e249-56.

Lim FS, Phua KB, Lee BW, *et al*. Safety and reactogenicity of DTaP-HBV- IPV/Hib and DTaP-IPV/I-Hib vaccines in a post-marketing surveillance setting. *Southeast Asian J Trop Med Public Health* 2011; 42: 138-47.

Lolekha S, Hiranchote A, Simasathien S. Safety and immunogenicity of combined or associated administration of PRP-T vaccine with diphtheria, tetanus and pertussis vaccine in Thai children. *J Trop Pediatr* 2001; 47: 24-9.

Long SS, Deforest A, Smith DG, Lazaro C, Wassilak SG. Longitudinal study of adverse reactions following diphtheria-tetanus-pertussis vaccine in infancy. *Pediatrics* 1990; 85: 294-302.

Principi N, Esposito S. Vaccines and febrile seizures. *Expert Rev Vaccines* 2013; 12: 885-92.

Sullivan JE, Farrar HC, the Section on Clinical Pharmacology and Therapeutics and Committee on Drugs. Fever and antipyretic use in children. *Pediatrics* 2011; 127: 580-7.

Thisyakorn U, Chotpitayasunondh T, Pancharoen C, Chuenkitmongkol S, Ortiz E. Evaluation of an acellular pertussis, diphtheria, tetanus, inactivated poliovirus, Hib-conjugate combined vaccine (Pentaxim) at 2, 4, and 6 months of age plus hepatitis B vaccine at birth, 2, and 6 months of age in infants in Thailand. *Southeast Asian J Trop Med Public Health* 2010; 41: 450-62.

Thisyakorn U, Pancharoen C, Chuenkitmongkol S, Ortiz E. Immunogenicity and safety of a DTaP-IPV//PRP-T vaccine (Pentaxim) booster during the second year of life in Thai children primed with an acellular pertussis combined vaccine. *Southeast Asian J Trop Med Public Health* 2009; 40: 282-94.

Tormans G, Van Doorslaer E, van Damme P, Clara R, Schmitt HJ. Economic evaluation of pertussis prevention by whole-cell and acellular vaccine in Germany. *Eur J Pediatr* 1998; 157: 395-401.

US Food and Drug Administration (FDA). Center for Biologics Evaluation and Research. September 2007. Guidance for the industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Silver Spring: FDA, 2007. [Cited 2013 Nov 23]. Available from: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidance/Vaccines/ucm074775.htm

US Food and Drug Administration (FDA). Safety. [Updated 2013 Aug 23]. Silver Spring: FDA, 2013. [Cited 2013 Nov 23]. Available from: http://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm

Waight PA, Pollock TM, Miller E, Coleman EM. Pyrexia after diphtheria/tetanus/pertussis and diphtheria/tetanus vaccines. *Arch Dis Child* 1983; 58: 921-3.

World Health Organization (WHO). Recommendations for whole cell pertussis vaccine. *WHO Tech Rep Ser* 2007; 941. [Cited 2015 Feb 18]. Available from: http://www.who.int/biologicals/publications/trs/areas/vaccines/whole_cell_pertussis/Annex%206%20whole%20cell%20pertussis.pdf

World Health Organization (WHO). Pertussis. Geneva: WHO, 2013a. [Cited 2015 Feb 18]. Available from: http://www.who.int/biologicals/vaccines/pertussis/en/

World Health Organization (WHO). Safety of Quinvaxem (DTwP-Hep B- Hib) pentavalent vaccine. Geneva: WHO, 2013b. [Cited 2013 Nov 23]. Available from: http://www.who.int/immunization_standards/vaccine_quality/quinvaxem_pqnote_may2013/en/

World Health Organization (WHO). Revised guidance on the choice of pertussis vaccines: Geneva: WHO, 2014. [Cited 2014 Sept 6]. Available from: http://www.who.int/wer/2013/wer8930.pdf?ua=1