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Global Vaccine Safety
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INFORMATION SHEET
OBSERVED RATE OF VACCINE REACTIONS
DIPHTHERIA, PERTUSSIS, TETANUS VACCINES

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The Vaccines

Diphtheria and tetanus toxoids have been combined with pertussis antigens and used as a combination DTP vaccine since the 1940s. More recently, this DTP combination has been used as the basis for the development of combination vaccines containing additional vaccine antigens added singly or in additional combinations such as *Haemophilus influenzae* type b, hepatitis B and inactivated poliovirus, allowing multiple vaccine antigens to be delivered via a single injection. In addition, in some DTP vaccines the diphtheria dose has been reduced and pertussis antigen has been modified to allow these vaccines to be used for booster doses in adolescents and adults. Because these toxoids and antigens are now frequently used as combined vaccines, most adverse events following immunization reported in these vaccines are likely due to the safety profile of their individual components.

Vaccine preparations:

Multiple combination vaccines to prevent diphtheria, tetanus, and pertussis are in use globally and each has a specific composition. Understanding how the toxoid and antigen contents are standardised and recorded is important when comparing different combination vaccines. For diphtheria and tetanus the potency and amount of toxoid in a vaccine are recorded in International Units (IU) and in Limits of Flocculation (Lf). Whole-cell pertussis vaccines are standardised using a mouse protection test. No simple methods exist for standardising the potency of acellular pertussis vaccines.
DTP vaccines are available in various formulations and are given in 0.5 mL doses. The five most common are DTwP, DTaP, Tdap, DT, and Td. Of these vaccines, three (DTwP, DTaP and DT) are given to children younger than 7 years of age, and two (Tdap and Td) are given to individuals 7 years or older. As indicated by the lower case "d" and "p", the concentration of diphtheria and pertussis toxoids has been reduced in these "adult" formulations to prevent adverse effects, while the "a" in "ap" indicates that the pertussis toxoids are acellular.

Composition of single antigen vaccines:

Diphtheria toxoid - Diphtheria toxoid is prepared by formalin inactivation of diphtheria toxin. Usually it is available as a preparation adsorbed with aluminium hydroxide or phosphate and combined with other toxoids or vaccine antigens. The potency of diphtheria vaccine used for the immunization of children should not be less than 30 IU per single human dose, while for adults; the potency is about a third of the dose for children. Monovalent single antigen diphtheria toxoid is currently commercially unavailable.

Tetanus toxoid - Tetanus toxoid is a preparation of formalin inactivated toxin. The toxoid is available adsorbed with aluminium phosphate or hydroxide, alone or in combination with other toxoids or vaccines. The potency of tetanus toxoid, expressed in International Units, varies widely according to the preparation and the manufacturer, but WHO stipulates the potency of tetanus vaccine used for the immunization of children should not be less than 40 IU per single human dose. The minimum potency specification for tetanus vaccine intended for booster immunization of older children and adults may be lower and should be approved by the National Regulatory Authority (NRA). Single antigen adsorbed tetanus toxoid is available with a toxoid content of 2 to 10 Lf/dose.

Pertussis antigens **-** Pertussis vaccines either contain antigens from the whole pertussis organism or a variable number of purified acellular component antigens. The whole-cell vaccines contain a suspension of killed *B. pertussis* organisms at a concentration of more than 4 IU. The acellular vaccines are made from purified antigens of *Bordetella pertussis*. All the current vaccines contain pertussis toxoid (3.2 to 40µg per dose) and most contain filamentous agglutinin (2.5 - 34.4 µg per dose). Additional antigens in these vaccines may include pertactin (1.6 - 23.4 µg per dose), fimbriae 2 (0.8 to 5 µg per dose) and fimbriae 3 (5 µg per dose), (CDC, 1997). Currently no pertussis vaccines are available that contain a combination of less than 2 vaccine antigens (Joyce, 1994).

Composition of DTP vaccines:

Although different combinations may contain the same toxoids or antigens each vaccine may differ substantially according to the toxoid or antigen dose, number of pertussis components (for acellular vaccines), method of purification and inactivation of the toxins and incorporation of adjuvants and excipients. All of these factors may have an impact on the reactogenicity of different DTP vaccine combinations.

Diphtheria and Tetanus (DT and Td) toxoid combination*:* DT vaccine used for primary immunisation and boosting in children contains 6.7-25Lf of diphtheria toxoid and 5 – 7.5 Lf of tetanus toxoid per dose. An adult combination, Td, is used for boosting and primary immunisation in adolescents and adults and contains a lower dose of diphtheria (less than 2 Lf/dose) but a similar dose of tetanus toxoid.

***Diphtheria, Tetanus and Pertussis (DTP) combinations**:* Initial DTP combination preparations contained whole-cell pertussis antigens. Concern due to common occurrence of minor local reactions and less common severe reactions of whole-cell pertussis led to the development of acellular vaccines and clinical trials demonstrating their efficacy in the 1980's. Multiple acellular pertussis vaccines are now available and are referred to by the number of acellular antigen components that they contain. Whole-cell pertussis vaccine remains a safe, inexpensive and effective vaccine which is used in many countries because whole cell vaccines that generate a higher level of antibody to pertussis toxin are associated with higher vaccine efficacy.

DTP with other vaccine antigen combinations: There are many vaccine formulations containing diphtheria and tetanus toxoids and whole cell or acellular pertussis antigens in combination with *Haemophilus influenzae* type b, hepatitis B and/or inactivated polio virus to produce quadrivalent, pentavalent and hexavalent combination vaccines.

Adverse events

Diphtheria toxoid vaccines

Initial use of diphtheria toxoid, was associated with significant local and systemic reactions but purifying the toxoid, adsorbing it on aluminium hydroxide enabled the reduction of the required toxoid dose. This decreased the frequency of such reactions. (Vitek CR et al., 2008). However, comprehensive safety data for the currently used adsorbed preparation of diphtheria toxoid is limited since monovalent diphtheria vaccine is seldom used. Most understanding about reactogenicity of diphtheria toxoid comes from comparisons between TT and TD/DT.

The frequency of reactions was related to three factors: the degree of purity of diphtheria toxoid, the dose of antigen, the number of previous booster doses and spacing from previous dose. Even highly purified toxoid, free of all traces of impurities can result in undesirable reactions in a high proportion of older immune persons probably related to hypersensitivity to diphtheria toxoid (Galazka et al., 1996), Systemic reactions seen in 3-10% of vaccinees after a 2-5 Lf dose included malaise, headache, or fever. A 10 Lf dose of diphtheria toxoid given to adult health workers caused common severe reactions (Butterworth et al 1974). Reactions were significantly correlated with the level of response to a booster dose. In persons with no adverse reactions, the mean antitoxin level was 0.48 IU per ml following a booster dose, compared with levels of 0.89 IU per ml in persons with local reactions, and 1.53 IU per ml in those with systematic reactions (Simonsen O et al., 1986).

Mild adverse events

The only data available is when the toxoid has been used as a booster dose in adults. Adults, primed with diphtheria in childhood and who received diphtheria vaccine containing 1.5 Lf of toxoid, commonly experience mild or moderate local reactions (38%). However, severe pain at the injection site was reported in 20%. Reactions to adsorbed diphtheria toxoid are more frequent among people who have already received several booster doses (Edsall et al., 1954). Their frequency varies with the toxoid concentration and the level of anti-diphtheria toxin antibodies present in the blood prior to vaccination. General symptoms (weakness of mild to moderate severity) was reported in 24% (Nahum et al., 1994 However, in a similar study using the same antigen content, but only including those individuals with a pre-vaccination antibody titre of less than 0.1IU/l, only 8% of subjects reported injection site pain. (Mortimer et al., 1986).

Severe adverse events

Severe adverse events solely attributable to diphtheria toxoid have not been documented. However, this relates in part to the current use of this antigen in combination vaccines and it is difficult to completely exclude diphtheria toxoid as being implicated in some of the rare severe adverse events following use of DTP combination vaccines.

Tetanus toxoid vaccines

Mild local reactions are common after tetanus toxoid; however more serious reactions are rare. The rates and severity are influenced by the number of prior doses, level of pre-existing antitoxin, the type and quantity of adjuvant, the route of injection and the presence of other substances as preservatives.

Mild adverse events

Local reactions are common and have been reported to occur in 50-80% of vaccine recipients who receive a booster dose. These manifest as erythema, oedema and pain (Wassilak, 2008). Extensive limb swelling is uncommon and occurs in less than 2% of vaccinees and is more likely in those who have received multiple booster doses (Relihan, 1969). The pathogenesis of these reactions is poorly understood and the serum level of anti-toxin does not predict which individuals maybe at increased risk. Systemic reactions attributed to booster injections occur in 0.5% to 10% of cases; such reactions entail fever, malaise, shivering, general aches and headaches. The intensity and frequency of local and systemic reactions to tetanus vaccination increase with age, with the number of doses administered and with the concentration of toxoid. The local reaction rate to the first injection of the basic immunization course was 0·9%, to the second injection 2·7%, and to the third injection 7·4%. To booster injections the rate was 1·6%. The local reaction rate was appreciably higher in women than in men – 14·4 % and 5·7 % respectively in the case of the third injection – and the incidence among women increased with age. (Myers et al., 1982; CDC, 1996; White WG et al., 1973).

Severe adverse events

Neurological events: Peripheral neuropathy, particularly brachial plexus neuritis, has been reported to occur hours to weeks after tetanus toxoid administration. Review of these case reports indicates that they are consistent with neuropathy as a manifestation of immune complex disease (Wassalik et al., 2008). Passive surveillance of events following immunization in the United States for 1991 – 2003 indicated that the ratio of the reported cases of brachial neuritis occurring 0 to over 60 days was 0.69 cases for 10 million doses (Zhou, 2004). Guillain-Barré syndrome (GBS) has been reported following TT vaccination. However, population studies that have examined the occurrence of GBS in children who have received DTP or TT vaccines do not support this vaccine as a cause of GBS (Tuttle et al., 1997). Other neurological events such as seizures have been reported but these are thought to be coincidental events rather than causal (Institute of Medicine Vaccine Safety Committee, 1994).

Allergic reactions: Anaphylaxis following TT is rare. Available incidence data came from studies performed in the 1940 to 1960s when TT vaccine may have been contaminated with other allergens (Cooke et al., 1940; Cunningham, 1940; Wassilak et al., 2008). Recent passive surveillance data demonstrate an anaphylaxis rate of 1.6 per 1,000,000 doses for Td vaccine (Wassilak et al., 2008). Skin testing with TT has not been useful in predicting the recurrence of anaphylaxis in individuals who present with a history of a possible hypersensitivity reaction to the vaccine. Severe local reactions can occur in hyper immunized persons and this is thought to be due to an Arthus-type hypersensitivity reaction (hypersensitivity to immune complexes) (Sutter, 1994).

Pertussis vaccine

There are no safety studies that have evaluated the safety of pertussis vaccine when used as the only vaccine antigen. The evidence that pertussis antigens account for a number of adverse events are derived from studies which have compared adverse events following DPT vaccination and DT vaccination. The adverse event information for pertussis is therefore presented under the section on DTP vaccine combinations below.

Adverse events following combination vaccines

Diphtheria and Tetanus (DT and Td) toxoid vaccines

A prospective study comparing the reactions 48 hours following DTwP and DT vaccine in children 0 – 6 years found that rates for DT vaccine was local redness, 7.6%, local swelling 7.6%, pain 9.9 %, fever 14.9 %, drowsiness 14.9 %, fretfulness 22.6%, vomiting 2.6 %, anorexia 7.0% and persistent crying 0.7%. (Cody et al., 1981) This was significantly lower than the rates for DTwP which were local redness, 37.4%, local swelling 40.7%, pain 50.9%, fever 31.5%, drowsiness 31.5%, fretfulness 53.4%, vomiting 6.2%, anorexia 20.9%and persistent crying 3.1% respectively.

In a prospective study to assess the reactogenicity of tetanus-diphtheria (adult-type) (Td) vaccine, with a mean age of 39 years (range 18- 85 years), overall, 50% of subjects reported some type of adverse reaction. This included pain 43%, discomfort with arm movement 14%, swelling 3.8%, malaise 5.1%, and fever (axillary temperature greater than or equal to 38 degrees C) 1.7%. Local and general reactions were considered as mild by almost two-thirds of vaccinees. Moderate plus severe local reactions more commonly reported in the 18 to 35 year old group than in the 36 to 65 year old group (Vilella et al., 2000).

Diphtheria, Tetanus and Pertussis (DTP) combinations

These vaccines contain Diphtheria, Tetanus and whole-cell Pertussis (DTwP) antigens. In general currently available combinations of DTwP with IPV, HepB and/or Hib do not result in adverse reactions that exceed, in frequency or severity, those seen with the same DTwP vaccine given alone (Decker et al., 2008).

Mild adverse events

Mild adverse events following DTwP when administered for both primary and booster immunisations in infants and children are common and consist of local reactions (50%) and systemic reactions such as fever over 38°C and irritability (40% to 75%), drowsiness (33% to 62%), loss of appetite (20% to 35%), and vomiting (6% to 13%) (Edwards KM et al., 2008).

The whole-cell component of pertussis is largely, but not solely, responsible for reactions occurring after administration of combined DTwP vaccine as demonstrated by studies that have compared the rates of adverse events after DTwP vs. DT and also DTwP vs. DTaP immunisation. (Cody, 1981; Feery, 1982; Long, 1990; Scheifele, 1994; Gupta, 1991; Cherry, 1996). A prospective study of adverse events 48 hours following DTP compared to DT vaccine in children 0 – 6 years showed that the reaction rates associated with DTwP vaccine were local redness, 37.4% local swelling, 40.7%; pain, 50.9%; fever, 31.5%; drowsiness, 31.5%; fretfulness, 53.4%; vomiting, 6.2%; anorexia, 20.9% and persistent crying, 3.1%. These were five times higher than the DT vaccine (Cody et al., 1981; Kathryn et al., 2008). Review of post-licensure passive surveillance data from the United States of America demonstrated that that the reporting rate of AEFI following DTwP vaccination is double that of DT vaccine (Stetler et al., 1985) - 70.8 per million doses administered vs. 38.4, respectively. These findings were consistent with clinical studies.

Studies have also compared the use of DTwP as a booster dose in 4-6 year old children and found the rates of severe local reactions (an area of redness or swelling or both of 50 mm or greater) 24 hours after vaccination to be higher after DTwP vaccination when compared with DT vaccination (Scheifele et al., 1994).

The frequency of local reactions tends to increase with the number of doses administered, while systemic reactions (Pollock et al.,1984; Cody et al., 1981) with the exception of fever (Cherry, 1996), may diminish with subsequent doses. Local reactions are also more likely when adsorbed vaccines are given subcutaneously rather than intramuscularly (Mark et al., 1999).

Severe adverse events

High fever. Temperature in excess of 40.5°C may occur in 0.3% of vaccine recipients (Blumberg et al., 1993).

Persistent crying. Some infants develop continuous crying which may be unaltered, inconsolable, and last for a number of hours. It is suggested that localized reaction may be a cause of persistent crying. A case definition has been proposed but definitions vary widely in reported studies (Bonhoeffer, 2004). Persistent crying (>1 hour) occurred in 3.5% of children after both DTwP and DT vaccination but was 4 times more common after DTwP vaccination (Cody et al., 1981). Persistent crying is more frequent with the initial dose and less frequent thereafter. This can vary with the lot of the vaccines (Larry et al., 1984).

Seizure. The rate of febrile seizures occurring within 3 days of DTwP vaccination has been shown to be reasonably consistent in clinical studies 60 per 100,000 doses and in active surveillance studies which have used data linkage 8 per 100,000 doses (Cody et al., 1981; Farrington et al., 1995). Febrile seizures after a DTwP vaccine are more common in those individuals with a personal history (with a relative risk of 6.4) or a family history (relative risk of 2.4) of seizures (Edwards et al., 1999; Livengood et al., 1989). Febrile seizures, are considered benign and do not result in epilepsy (Cody et al., 1981; Gale et al., 1990).

Hypotonic–hyporesponsive episode (HHE). A case definition defines an HHE as the sudden onset of limpness and reduced responsiveness and pallor or cyanosis (Buettcher et al., 2007). In 1991 the review by the Institute of Medicine concluded that there was sufficient evidence available to establish a causal relationship between whole-cell pertussis vaccine and HHE (IOM 1991). Although HHE occurs most frequently after whole-cell pertussis vaccine the reaction has been documented to occur after other vaccines, including diphtheria, tetanus, *Haemophilus influenzae* type b and hepatitis B (Cody, 1981; Braun, 1988). The reported rates following a whole cell pertussis vaccine ranges from 0 - 291 per 100,000 doses (Cody et al., 1981; DuVernoy et al., 1999, Chen et al., 2000). The cause is not known but recovery occurs spontaneously and no long term sequelae have been documented (Braun et al., 1998). A number of studies have reported on the follow up of HHE cases (Gold R et al., 1997, Heijbel H et al., 1999). However these studies have relied on parental reporting rather than formal neurodevelopmental testing (with the exception of the study by Baraff et al., 1984). The conclusion of this study was that there was no evidence that any of these children had any evidence of serious neurological damage associated with the HHE. The majority of these infants can be safely re-vaccinated without a recurrence of the HHE (Vermeer-de Bondt et al.,1998; Goodwin et al., 1999). In addition, the advent of acellular pertussis vaccines has markedly decreased the frequency of episodes of HHE (LeSaux et al., 2003).

Encephalopathy. The occurrence of encephalopathy after whole-cell pertussis vaccination has been an issue of intense scrutiny and debate. Often cited are the National Childhood Encephalopathy Study conducted in UK from 1976 to 1979 and the Institute of Medicine (IOM) report (1994). The initial findings of the National Encephalopathy study were that acute encephalopathy occurred at a rate of 1 per 310,000 to 5,300,000 doses (95% CI 54,000 to 5,310,000). Subsequent investigations and follow-up of the affected children then cast some doubt on these initial findings and demonstrated no increase in the rate of death or other sequelae after a DTwP vaccine (Edwards et al., 2008). However, despite these revised findings this has been an area of ongoing controversy. In 1994, the IOM concluded that "the balance of evidence is consistent with a causal relationship between DTwP and chronic nervous system dysfunction in children whose serious acute neurological illness occurred within 7 days of a DTwP vaccination". This may imply that the vaccine rarely may trigger such an event in an individual who may be predisposed to develop such a condition because of an underlying abnormality. The IOM committee concluded that the evidence is insufficient to indicate either the presence or absence of a causal relationship between DTwP vaccine and permanent neurological damage (Cowan et al.,1993).

More recent studies do not confirm an association between DTwP and acute encephalopathy. A population-based case-control study has evaluated the association between serious acute neurological illness and receipt of whole-cell pertussis vaccine, given as diphtheria-tetanus-pertussis (DTwP) vaccine. The estimated odds ratio for children with encephalopathy or complicated seizures was 3.6 (95% CI, 0.8 to 15.2). The study concluded that there was no statistically significant increased risk of serious acute neurological illness in the 7 days after DTwP vaccine exposure (Gale et al., 1994). A retrospective case-control study performed at four health maintenance organizations by examining children aged 0 to 6 years who were hospitalized with encephalopathy or related conditions determined that cases were no more likely than controls to have received a DTwP vaccine during the 90 days before disease onset. When encephalopathy of known etiology was excluded, the odds ratio for case children having received DTP within 7 days before onset of disease was 1.22 (95% CI, 0.45-3.31, P = 0.693) compared with control children. The study concluded that DTwP vaccination was not associated with an increased risk of encephalopathy (Ray et al., 2006).

Dravet's Syndrome. Dravet's syndrome (DS), otherwise known as severe myoclonic epilepsy of infancy (SMEI), is an epileptic encephalopathy presenting in the first year of life. DS has a genetic etiology. It is observed that between 70% and 80% of patients carry sodium channel α1 subunit gene (SCN1A) abnormalities, and truncating mutations account for about 40% and have a significant correlation with an earlier age of seizures onset. Seizures following vaccinations have been reported in 27% of cases with Dravet's syndrome. In 58% of these patients vaccination-related seizures represented the first clinical manifestation. The majority of seizures occurred after DTwP vaccinations and within 72 h after vaccination (Tro-Baumann et al., 2011).

Anaphylaxis. Anaphylactic events are rare; however there has been little consistency in defining this event. A case definition for this event has recently been proposed (Ruggeberg et al., 2007). A data linkage study showed a rate of 0.13 (CI 0.003 to 0.71) cases per 100,000 administered doses of DTwP vaccine (Edwards et al., 1999; Bohlke, 2003). The study population were children and adolescents enrolled in a Health Maintenance Organisation. Cases were initially ascertained by data linkage of vaccine records according to ICD coding for anaphylaxis. Case notes were reviewed and classified as anaphylaxis according to the onset of symptoms, organ systems involved and treatment.

Other. There have been isolated case reports of brachial neuritis after DTwP vaccine (Hamati-Haddad et al..1997).

Vaccines containing Diphtheria, Tetanus and Acellular pertussis (DTaP)

Multiple vaccines have combined acellular pertussis antigens with Diphtheria and Tetanus toxoid. These vaccines have varied in the number and quantity of pertussis antigens but in general this does not affect the rate or type of adverse events reported after these vaccine combinations (Englund et al.,1994, Decker et al., 1995). For this reason DTaP vaccines are considered together.

Mild adverse events

Mild adverse events are similar but less frequent following vaccines containing acellular pertussis antigens compared to vaccines containing whole-cell pertussis antigens (Decker et al., 1995; Stehr et al., 1998; Edwards et al., 1999; CDC, 1997). One particular study that compared 13 acellular pertussis vaccines and one whole-cell pertussis vaccine, and adverse event results are presented in Table 1. Studies have also shown that the frequency of reactions containing the acellular component of pertussis does not exceed the frequency following injection of a vaccine without the pertussis component (DT or Td vaccines) (Gustafsson et al., 1996).

For booster doses of DTaP there is an increased likelihood of local reactions that included extensive limb swelling with subsequent doses (Gold et al., 1999). In a randomized clinical trial, the rates of injection site redness $\geq$ 50mm were similar in recipients of five doses of acellular pertussis vaccine (32.8%) or five doses of whole-cell pertussis vaccine (43.3%). Injection site swelling, tenderness, and decreased arm movement were all more frequent in children who received five doses of whole-cell pertussis vaccine (Halperin et al., 2003). Local adverse reactions after booster immunization with acellular vaccine are more common in children primed with acellular vaccine than those primed with whole cell vaccine (68% vs. 33%; relative risk, 2.1; 95% confidence interval, 1.3 to 3.3) (Halperin et al., 1995).

Severe adverse events

Local events - Extensive limb swelling may occur in 2-6% of vaccinees, after booster (4th and 5th) doses of the DTaP vaccine. Although these reactions may cause swelling which may involve the entire vaccinated limb, they resolve spontaneously and do not lead to any sequelae (Rennels, 2003).

General adverse events - For primary immunisation, as for mild events, severe adverse events occurring after DTaP are similar in nature to those that occur after DTwP but occur less frequently. Seizures, persistent crying, HHE, and fever in excess of 40°C have all been reported (Edwards et al., 1999). Several studies have demonstrated the safety of substituting a vaccine containing the acellular pertussis component as a booster for a child who began the course of vaccination with a vaccine containing the whole cell component (Pichichero et al., 1997; Halperin et al., 1996; Feldman et al., 1992).

DTP vaccines with other combinations

As indicated earlier, an increasing number of combination vaccines are being developed and used in many countries and these vaccines include other antigens such as Haemophilus influenzae type b, hepatitis B and IPV.

Clinical trials have not shown any increase in adverse events with an increasing number of vaccine antigens. Fairly soon after their introduction, isolated case reports have been reported of unexpected death after hexavalent DTP vaccine. A number of studies however failed to confirm this, including a large case control study with immunisation data on 307 SIDS cases and 971 controls which did not find any increase in the risk of SIDS in the 14 days following immunisation (Vennemann et al., 2007).

Table 1: Percentage of mild reactions by the third day following a dose of DTP vaccine[#]

Adverse reactions	Acellular vaccines % All DTaP tested (range)				Whole Cell Vaccines %			
Dose	First	Second	Third	Any	First	Second	Third	Any
Fever 37.8 to 38.3	3.8 (1.6 - 7.3)	10.1 (4.4-17.9)	13.6 (9.7-22.8)	20.8 (16.0-29.2)	24.3	28.8	27.8	44.5
Fever 38.4 to 38.9	0.3 (0-1.6)	0.8 (0-1.8)	1.7 (0-3.5)	2.8 (1.6-4.2)	3.0	3.9	7.3	12.4
Fever ≥ 40	0.1 (0-0.9)	0.4 (0-0.9)	0.5 (0-1.7)	0.9 (0-1.7)	0.0	1.4	2.6	3.5
Redness 1 - 20 mm	12.2 (4.4-20.2)	16.2 (9.6-27.6)	19.8 (9-25.8)	31.4 (15.1-44)	40.8	41.6	44.4	56.3
Redness > 20 mm	1.3 (0-2.9)	0.9 (0-3.8)	1.7 (0-3.8)	3.3 (1.4-5.9)	8.6	6.1	3.2	16.4
Swelling 1 - 20 mm	7 (9.7-4.1)	10.7 (4.4-16.5)	11.1 (5.4-18.4)	20.1 (10.9-28.6)	23.2	24.6	30.1	38.5
Swelling > 20 mm	1.7 (0-4.2)	1.4 (0-3.6)	2.2 (0-6)	4.2(0.8-8.0)	16.5	9.5	5.6	22.4
Pain Moderate*	3.6 (1.6-7.4)	1.9 (0-5.1)	2 (0-3.8)	6.5 (1.6-12.5)	17.6	12.6	12.0	25.6
Pain Severe	0.2 (0-4.7)	0.1 (0-0.9)	0.1(0-0.9)	0.4 (0-1.7)	9.7	6.1	3.8	14.3
Fussiness Moderate@	4.6 (2.5-7.4)	6.1 (4.1-10.2)	5.4 (1.9-8.5)	12.4 (8.4-20.2)	16.8	16.5	12.6	29.1
Fussiness Severe	2 (0.7-3.7)	1.6 (0-4.9)	1.3 (0-3.5)	4.7 (1.5-8.0)	3.8	7.0	4.7	12.4
Drowsiness	29.9 (19.3-37.5)	17.6 (10.5-26.7)	12.9 (4.6-18.1)	42.7 (29.4-52.2)	43.5	31.0	24.6	62.0
Anorexia	9.3 (7.5-13)	8.9 (4.5-13.5)	8.9 (3.9-12.3)	21.7 (17.7-27.2)	19.5	16.5	14.3	35.0
Vomiting	6.3 (3-12.9)	4.5 (1.5-10.6)	4.2 (0.9-7.5)	12.6 (7.4-21.6)	7.0	4.5	5.3	13.7

#13 different acellular pertussis vaccines, each containing 1 to 4 antigens, all combined with diphtheria and tetanus toxoids.
b) Whole-cell pertussis vaccine combined with diphtheria and tetanus toxoids. Source: Decker et al., 1995.
* Pain moderate: cried or protested to touch; severe: cried when leg moved
@ Fussiness moderate: prolonged crying and refused to play; severe, persistent crying and could not be comforted.

Table 2: Summary of serious adverse events after DTP vaccine

Description	Acellular DTP vaccines Rate/doses	Whole cell vaccines Rate/doses
Persistent screaming	0-0.2 per 100 b	3.5 per 100
Hyporesponsive hypotonic episodes	14-62 per 100,000 c	57-250 per 100,000
Seizures	0.5 per 100,000 d	6 per 100,000
Encephalopathy	No documented risk	0.3 - 5.3 per 1,000,000 a
Anaphylaxis	Rate undocumented	1.3 per 1,000,000 a

a - See comments in paragraph
b - Edwards K et al. 2008
c - Extrapolated from Scheifele D et al. 1998
d - Rosenthal et al. 1996.

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