24

Pertussis

NOTIFIABLE

The disease

Whooping cough (pertussis) is a highly infectious disease that is usually caused by *Bordetella pertussis*. A similar illness is caused by *B. parapertussis*, but this is not preventable with presently available vaccines.

There is an initial catarrhal stage, followed by an irritating cough that gradually becomes paroxysmal, usually within one to two weeks. The paroxysms are often followed by a characteristic 'whoop' or by vomiting. In young infants, the typical 'whoop' may never develop and coughing spasms may be followed by periods of apnoea. The illness often lasts for two to three months. In older children and adults, the disease may present as persistent cough without these classic symptoms and therefore not be recognised as whooping cough.

Pertussis may be complicated by bronchopneumonia, repeated vomiting leading to weight loss, and cerebral hypoxia with a resulting risk of brain damage. Severe complications and deaths occur most commonly in infants under six months of age. Minor complications include subconjunctival haemorrhages, epistaxis (nosebleeds), facial oedema, ulceration of the tongue or surrounding area, and suppurative otitis media.

Transmission of the infection is by respiratory droplet, and cases are most infectious during the early catarrhal phase. The incubation period is between six and 20 days and cases are infectious from six days after exposure to three weeks after the onset of typical paroxysms.

History and epidemiology of the disease

Before the introduction of pertussis immunisation in the 1950s, the average annual number of notifications exceeded 120,000 in England and Wales (Figure 24.1).

By 1972, when vaccine coverage was around 80%, there were only 2,069 notifications of pertussis. Because of professional and public anxiety about the safety and efficacy of the whole-cell vaccine, coverage fell to about 60% in 1975 and reduced further to reach around 30% by 1978. Major epidemics occurred in 1977–79 and 1981–83. In 1978 there were over 65,000 notifications and 12 deaths (Amirthalingam *et al*., 2013). These two major epidemics illustrate the impact of a fall in coverage of an effective vaccine. The actual number of deaths due to these pertussis outbreaks was higher, since not all cases in infants are recognised (Miller and Fletcher, 1976; Crowcroft *et al*., 2002) but with current surveillance systems, under ascertainment of deaths from diagnosed pertussis cases is now considered to be small (van Hoek *et al*., 2013b).

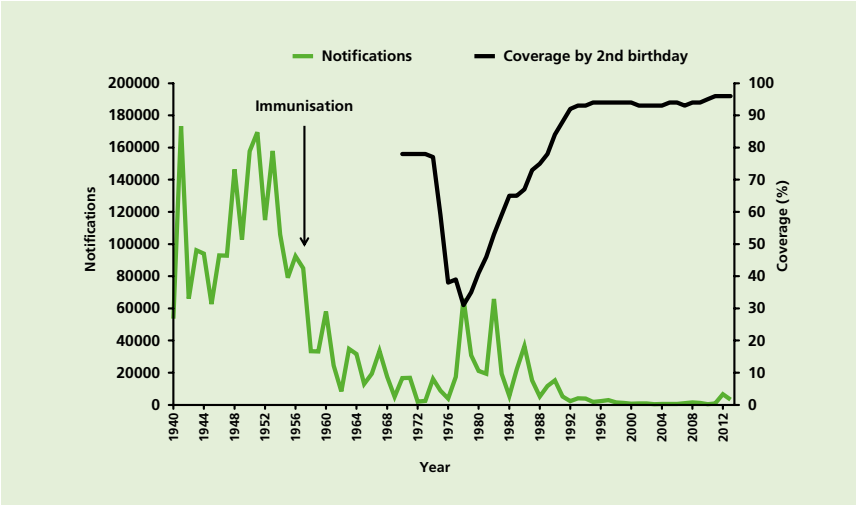

Figure 24.1 Pertussis notifications (England and Wales) and vaccine coverage (England only) of children by their second birthday (1940–2013)

The return of professional and public confidence increased vaccine uptake. Since 1992, coverage has been consistently 92% or higher by the second birthday and pertussis notifications fell to fewer than 5,000 per year. During the period 2000-2011 there were 1,500 cases or less notified annually. In recent years, the introduction of new diagnostic methods, and widespread use of serology testing in particular, has improved the ascertainment of laboratory confirmed pertussis in older children and adults.

Despite sustained levels of vaccine coverage above 95% from 2010, an increase in pertussis activity was observed in England and Wales from October 2011 and continued into 2012, initially affecting adolescents and adults and later extending to young infants. As a result, a national outbreak was declared in April 2012. Several other countries with longstanding vaccination programmes, including Australia, Canada and the United States, have also experienced increased pertussis activity in recent years. The reasons for the resurgence in disease in the presence of sustained high vaccine coverage are unclear but potential explanations include improved case ascertainment, the change from whole-cell to acellular vaccines, waning immunity and genetic changes in *B. pertussis* (Cherry, 2012).

Pertussis in the very young is a significant cause of illness and death. The majority of hospitalisations occur in infants under six months of age, some of whom are seriously ill and require admission to paediatric intensive care units (Crowcroft *et al.*, 2003). During the period 2001-2011, there were 48 deaths due to pertussis in infants of less than one year of age in England. Of these deaths, 41 occurred in infants who were too young to be protected by vaccination (van Hoek *et al*., 2013b). Adults and older children can be an important source of infection for young infants who are too young to be immunised (Crowcroft *et al*., 2003; van Hoek *et al*., 2013a) and contribute to sustained transmission (Campbell *et al*., 2014).

During the 2012 pertussis outbreak, the highest incidence of disease was among infants <3 months of age (Figure 24.2). Most infant cases became ill before they were old enough to receive their first dose of vaccine (Figure 24.3). In response to this outbreak, in October 2012 the Department of Health introduced a temporary programme to offer pertussis vaccination to pregnant women ideally between 28-32 weeks (but up to 38 weeks) of their pregnancy. This programme passively protects infants, through intrauterine transfer of maternal antibodies, from birth until they can be actively protected by the routine infant vaccination programme (Amirthalingam *et al*., 2014). In February 2016 JCVI advised that maternal pertussis immunisation can take place from week 16 of pregnancy (Eberhardt *et al*., 2016; JCVI February 2016 minute).

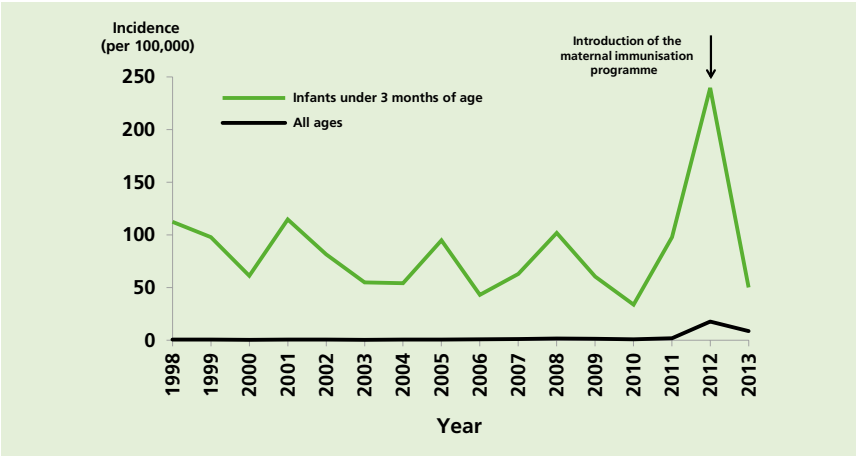

Figure 24.2 Incidence of laboratory confirmed cases of pertussis, England (1998-2013)

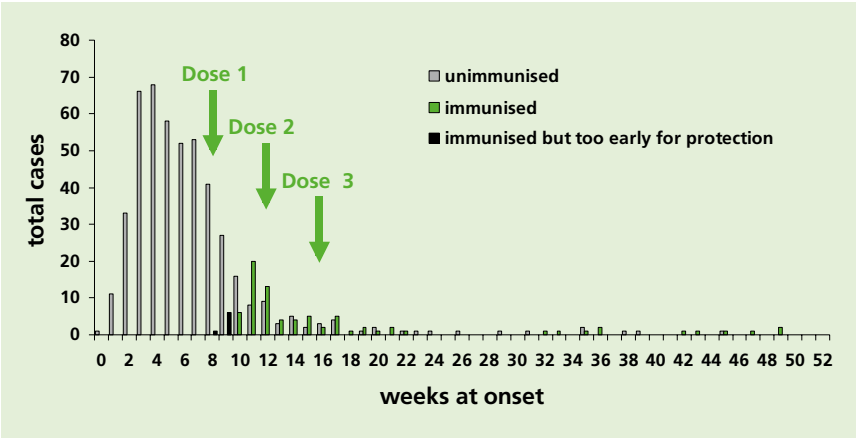

Figure 24.3 Onset age of pertussis cases in infants. Confirmed cases of pertussis in infants aged under one year old, by week of age at onset (2011-August 2012). Protection is assumed to accrue within the two weeks following immunisation.

Since its introduction the maternal pertussis immunisation programme has been shown to be very effective in protecting infants until they can have their first vaccinations at two months of age. During the first year of the programme, the average vaccine coverage in England was 64% and vaccine effectiveness was estimated to be 91% (Amirthalingam et al., 2014). A subsequent case-control study conducted in England and Wales showed that the adjusted vaccine effectiveness was 93% (Dabrera et al., 2014). During 2012, fourteen

infant deaths were reported in England and Wales and all deaths occurred in infants who were born before the introduction of the programme. Up to 31 October 2014, 10 deaths were reported in infants with confirmed whooping cough who were born after the introduction of the maternal programme. Nine of these 10 infants were born to unvaccinated mothers and all 10 infants were too young to have received their first dose of pertussis-containing vaccine and be fully protected by vaccination themselves (Public Health England, 2014).

Due to the success of the maternal vaccination programme in protecting infants and evidence of the safe use of acellular pertussis vaccine in the maternal programme (Donegan *et al*., 2014), in June 2014 the Joint Committee on Vaccination and Immunisation (JCVI) advised that this temporary programme should continue for at least a further five years.

https://www.gov.uk/government/publications/vaccine-update-issue-217-july-to-august-2014

Information on the pertussis maternal vaccination programme can be accessed here:

https://www.gov.uk/government/publications/whooping-cough-vaccination-programme-for-pregnant-women-extension-to-2014

https://www.gov.uk/government/publications/resources-to-support-whooping-cough-vaccination

https://www.gov.uk/government/publications/vaccine-update-issue-215-may-2014

Information and training resources for healthcare professionals on the pertussis maternal vaccination programme can be accessed here:

https://www.gov.uk/government/publications/vaccination-against-pertussis-whooping-cough-for-pregnant-women

The pertussis vaccination

The acellular vaccines are made from highly purified selected components of the *Bordetella pertussis* organism. These components are treated with formaldehyde or glutaraldehyde and then adsorbed onto adjuvants, either aluminium phosphate or aluminium hydroxide, to improve immunogenicity.

Acellular vaccines differ in source, number of components, amount of each component, and method of manufacture (Table 24.1), resulting in differences in efficacy and in the frequency of adverse effects (Edwards and Decker, 2013). The incidence of local and systemic reactions is lower with acellular pertussis vaccines than with whole-cell pertussis vaccines (Miller, 1999; Andrews *et al*., 2010).

Table 24.1 Composition of pertussis antigen-containing vaccines and therapeutic indications. Data extracted from Summary of Product Characteristics documents (August 2014). Vaccine composition based on a 0.5ml dose.

Vaccine	Diphtheria toxoid	Tetanus toxoid	Pertussis antigens	Inactivated poliovirus (produced/propagated in VERO cells)	*Haemophilus influenzae* type b polysaccharide
Pediacel® • Licensed from 6 weeks to 4 years of age • Supplied for primary immunisation from 01/10/04	≥ 30 IU*	≥ 40 IU*	Pertussis toxoid 20µg* Filamentous haemagglutinin 20µg* Pertactin 3µg* Fimbrial agglutinogens types 2&3 5 µg*	Type 1 40 D antigen units Type 2 8 D antigen units Type 3 32 D antigen units	Polyribosylribitol phosphate (10 µg) conjugated to tetanus toxoid (18-30µg)
	*Adsorbed on aluminium phosphate Excipients: phenoxyethanol, polysorbate 80, water for injection Trace amounts: formaldehyde, glutaraldehyde, streptomycin, neomycin, polymyxin B, bovine serum albumin				
Infanrix®-IPV+Hib • Licensed from 2 months of age • Supplied for primary immunisation from 01/06/14	≥ 30 IU*	≥ 40 IU*	Pertussis toxoid 25µg* Filamentous haemagglutinin 25µg* Pertactin 8µg*	Type 1 40 D antigen units Type 2 8 D antigen units Type 3 32 D antigen units	Polyribosylribitol phosphate (10 µg) conjugated to tetanus toxoid (30µg)
	*Adsorbed on aluminium hydroxide Excipients: lactose, medium 199, sodium chloride, water for injection Trace amounts: neomycin, polymyxin, polysorbate 80				
Repevax® • Licensed as a booster from 3 years of age • Supplied for pre-school booster from 27/09/04 • Supplied for pregnancy programme from 01/10/12 to 30/6/14	≥ 2 IU*	≥ 20 IU*	Pertussis toxoid 2.5µg* Filamentous haemagglutinin 5µg* Pertactin 3µg* Fimbrial agglutinogens types 2&3 5µg*	Type 1 40 D antigen units Type 2 8 D antigen units Type 3 32 D antigen units	
	*Adsorbed on aluminium phosphate Excipients: phenoxyethanol, polysorbate 80, water for injection Trace amounts: formaldehyde, glutaraldehyde, streptomycin, neomycin, polymyxin B, bovine serum albumin				
Infanrix®-IPV • Licensed as a booster from 16 months to 13 years of age • Supplied for pre-school booster from 27/09/04	≥ 30 IU*	≥ 40 IU*	Pertussis toxoid 25µg* Filamentous haemagglutinin 25µg* Pertactin 8µg*	Type 1 40 D antigen units Type 2 8 D antigen units Type 3 32 D antigen units	
	*Adsorbed on aluminium hydroxide Excipients: medium 199, sodium chloride, water for injection Trace amounts: neomycin, polymyxin, formaldehyde				
Boostrix®-IPV • Licensed as a booster from 4 years of age • Supplied for pregnancy programme from 01/07/14	≥ 2 IU*	≥ 20 IU*	Pertussis toxoid 8µg* Filamentous haemagglutinin 8µg* Pertactin 2.5µg*	Type 1 40 D antigen units Type 2 8 D antigen units Type 3 32 D antigen units	
	*Adsorbed on aluminium hydroxide & aluminium phosphate Excipients: medium 199, sodium chloride, water for injection Trace amounts: neomycin, polymyxin				

When the UK primary immunisation programme changed from whole-cell to acellular pertussis vaccines in 2004, a five component vaccine (Pediacel®), which contains pertussis toxoid (PT), filamentous haemagglutinin (FHA), fimbrial agglutinogens (FIM) 2 and 3, and pertactin (PRN) was chosen. This vaccine had been shown to offer equal or better protection against clinically typical pertussis disease than the whole-cell pertussis vaccine previously used in the UK (Miller, 1999). Although a three-component vaccine (Infanrix®IPV+Hib) containing PT, FHA and PRN was available for primary immunisation, this was not used because of limited data on efficacy. Subsequent analysis suggested that the cohorts who had Infanrix®+Hib, a similar vaccine with the same 3aP components, which was used in the UK in 1999-2001 because of a shortage of whole-cell vaccine, were as well protected up to the age of the pre-school booster as those cohorts who had been eligible for whole-cell or 5aP vaccines in infancy (Campbell *et al*., 2012). In 2008, therefore, the JCVI advised that a change to a three-component pertussis vaccine for primary immunisation was unlikely to have a discernible effect on pertussis epidemiology, particularly as 3-component vaccines were already being used as a pre-school booster. In 2010, the World Health Organisation reviewed all the global data on pertussis control in countries using acellular vaccines. They concluded that acellular pertussis vaccines with three or more components have higher protective efficacy than vaccines with fewer components, but did not find consistent evidence of a difference between three and five components (World Health Organisation, 2010). On the basis of this evidence, both three- and five-component pertussis-containing vaccines are now considered suitable both for primary immunisation and for pre-school boosting in the UK.

The pertussis vaccines are only given as part of combined products:

- diphtheria/tetanus/acellular pertussis/inactivated polio vaccine/ *Haemophilus influenzae* type b (DTaP/IPV/Hib) – for primary immunisation
- diphtheria/tetanus/acellular pertussis/inactivated polio vaccine/ (DTaP/IPV or dTaP/IPV) - for pre-school boosters
- diphtheria/tetanus/acellular pertussis/inactivated polio vaccine (dTaP/IPV) - for pregnant women.

The products used for boosting in older individuals will have lower antigen content for diphtheria, tetanus and pertussis antigen than the equivalent used for primary vaccination. It is important that primary vaccination in children is undertaken using a product with higher doses of pertussis, diphtheria and

tetanus antigens (Infanrix®IPV+Hib or Pediacel®) to ensure that adequate priming occurs. For adults, including pregnant women, a vaccine containing low dose diphtheria and tetanus (Repevax® or Boostrix®-IPV) should be used to avoid the higher rate of side effects observed with full dose preparations. For boosting primed children at the pre-school age, products with higher or lower doses of diphtheria, tetanus and pertussis antigens can be used (Infanrix®-IPV or Repevax®).

The above vaccines are thiomersal-free. They are inactivated, do not contain live organisms and cannot cause the diseases against which they protect.

Monovalent pertussis vaccines are not available.

Storage

Vaccines should be stored in the original packaging at +2˚C to +8˚C and protected from light. All vaccines are sensitive to some extent to heat and cold. Heat speeds up the decline in potency of most vaccines, thus reducing their shelf life. Effectiveness cannot be guaranteed for vaccines unless they have been stored at the correct temperature. Freezing may cause increased reactogenicity and loss of potency for some vaccines. It can also cause hairline cracks in the container, leading to contamination of the contents. For further information on storage, see **Chapter 3**.

Presentation

All vaccines containing pertussis antigens are available only as part of combined products (Table 24.1).

Pediacel®, Repevax®, Boostrix®-IPV and Infanrix®-IPV are supplied as cloudy white or off-white suspensions in pre-filled syringes. The suspensions may sediment during storage and should be shaken to distribute the suspensions uniformly before administration.

Infanrix®-IPV+Hib is supplied as a powder in a vial and a suspension in a pre-filled syringe. The vaccine must be reconstituted by adding the entire contents of the pre-filled syringe (containing DTaP-IPV suspension) to the vial containing the powder (Hib). The full reconstitution instructions are given in the Infanrix®-IPV+Hib Summary of Product Characteristics. After reconstitution, the vaccine should be injected immediately.

Dosage and schedule

All pertussis-containing vaccines are supplied as single doses of 0.5 ml.

Routine childhood immunisations

For the routine childhood immunisation schedule:

- First dose of 0.5ml of a pertussis-containing vaccine at two months of age
- Second dose of 0.5ml at three months of age (one month after the first dose)
- Third dose of 0.5ml at four months of age (one month after the second dose)
- A fourth dose of 0.5ml should be given as part of the pre-school booster (three years four months old or soon after).

Data on interchangeability are limited and so, wherever possible, the same DTaP-containing vaccine product should be used for all three doses of the primary vaccine course. If this is not possible, whichever primary vaccine is available (Pediacel® or Infanrix®-IPV+Hib) should be used. Vaccination should not be delayed because the vaccine used for previous doses is unavailable or not known.

Both Repevax® (dTaP/IPV) and Infanrix®-IPV (DTaP/IPV) are suitable for the pre-school booster vaccination, regardless of the vaccine used for primary vaccination.

Prenatal vaccination

Pregnant women should be offered a single 0.5 ml dose of dTaP/IPV vaccine. Vaccine should be offered to women in every pregnancy. Vaccination should be offered between gestational weeks 16 and 32 to maximise the likelihood that the baby will be protected from birth. For operational reasons, vaccination is probably best offered on or after the foetal anomaly scan at around 20 weeks. Women may still be immunised after week 32 of pregnancy but this may not offer as high a level of passive protection to the baby. Vaccination late in pregnancy may, however, directly protect the mother against disease and thereby just reduce the risk of exposure to her infant.

Both Boostrix®-IPV and Repevax® (dTaP/IPV) are suitable for vaccination in the prenatal programme. Boostrix-IPV is licensed for boosting from 4 years of age and therefore can only be used in the maternal programme, Repevax® (dTaP/IPV) may also be used as the pre-school booster. Providers should order and use the vaccine being supplied for the prenatal programme; this should be

documented on Immform or communicated in professional letters. In those exceptional circumstances when a woman attends and neither Boostrix®-IPV nor Repevax® (dTaP/IPV) is available, Infanrix®-IPV (DTaP/IPV) should be given rather than delay vaccination.

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/338567/PHE_pertussis_in_pregnancy_information_for_HP_2014_doc_V3.pdf.

Administration

Vaccines are routinely given intramuscularly into the upper arm or antero-lateral thigh. This is to reduce the risk of localised reactions, which are more common when vaccines are given subcutaneously (Mark *et al.*, 1999; Diggle and Deeks, 2000; Zuckerman, 2000). However, for individuals with a bleeding disorder, vaccines should be given by deep subcutaneous injection to reduce the risk of bleeding.

Pertussis-containing vaccines can be given at the same time as other vaccines such as MMR, PCV, MenC and hepatitis B. The vaccines should be given at a separate site, preferably in a different limb. If given in the same limb, they should be given at least 2.5cm apart (American Academy of Pediatrics, 2003). The site at which each vaccine was given should be noted in the patient's records.

Pertussis vaccine can be given to pregnant women at the same time as influenza vaccine but pertussis vaccination should not be given earlier than 16 weeks as this may compromise the passive protection of the infant against pertussis. Ideally pertussis vaccination should be offered from around 20 weeks, at the same time or after the foetal anomaly scan.

Disposal

Equipment used for vaccination, including used vials, ampoules or syringes, should be disposed of by placing it in a proper, puncture-resistant 'sharps' box according to local authority regulations and guidance in *Health Technical Memorandum 07-01: Safe management of healthcare waste* (Department of Health, 2013).

Recommendations for the use of the vaccine

The objective of the childhood immunisation programme is to provide a minimum of four doses of a pertussis-containing vaccine at appropriate intervals for all individuals up to ten years of age. To fulfil this objective,

the appropriate vaccine for each age group is determined also by the need to protect individuals against diphtheria, tetanus, Hib and polio.

The objective of the maternal vaccination programme is to provide a single dose of pertussis-containing vaccine for pregnant women from 16 weeks to 32 weeks of each pregnancy.

Primary immunisation

Infants and children under ten years of age

The primary course of pertussis vaccination consists of three doses of a pertussis-containing product with an interval of one month between each dose. DTaP/IPV/Hib is recommended for all infants from two months up to ten years of age. If the primary course is interrupted it should be resumed but not repeated, allowing an interval of one month between the remaining doses. DTaP/IPV/Hib should be used to complete a primary course that has been started with a whole-cell or another acellular pertussis preparation.

Children of one to ten years who have completed a primary course (which includes three doses of diphtheria, tetanus and polio), but have not received three doses of a pertussis-containing vaccine should be offered an extra dose of combined DTaP/IPV (or DTaP/IPV/Hib) vaccine to provide some priming against pertussis. The dTaP/IPV vaccine, which contains a lower dose of pertussis antigen, should only be used as a booster in fully primed children. They should then receive the first reinforcing dose as scheduled, also as DTaP/IPV (or DTaP/IPV/Hib), preferably allowing a minimum interval of one year.

Similarly, children who present for the pre-school booster without having received any pertussis vaccine previously should also receive DTaP/IPV (or DTaP/IPV/Hib). They should be given two doses – a priming and a reinforcing dose, preferably allowing a minimum interval of one year between doses.

Children of one to ten years who have completed the primary course plus a reinforcing dose (which includes four doses of diphtheria, tetanus and polio), but have not received four doses of pertussis-containing vaccine, may be offered an extra dose of combined DTaP/IPV or DTaP/IPV/Hib (if appropriate) to provide some or additional protection against pertussis. Compared to children who have followed the standard schedule, these children will receive an extra dose of diphtheria, tetanus and polio vaccines. Such additional doses are unlikely to produce an unacceptable rate of reactions (Ramsay *et al*., 1997).

Children aged ten years or over, and adults

Currently routine immunisation against pertussis is not recommended for those aged ten years and over, except for pregnant women (see below) or as part of outbreak control (see below).

Reinforcing immunisation

Children under ten years of age should receive the first pertussis booster combined with diphtheria, tetanus and polio vaccines. Either of the recommended pre-school vaccines should be used to boost a primary course of whole-cell or acellular pertussis preparations. The first booster of pertussis-containing vaccine should ideally be given three years after completion of the primary course, normally around three years and four months.

When primary vaccination has been delayed, this first booster dose may be given at the scheduled visit provided it is at least one year since the third primary dose. This will re-establish the child in the routine schedule. dTaP/IPV or DTaP/IPV should be used in this age group.

If a child attends for a booster dose and has a history of receiving a vaccine following a tetanus-prone wound, attempts should be made to identify which vaccine was given. If the vaccine given was the same as that due at the current visit and at an appropriate interval, then the booster dose is not required. Otherwise, the dose given at the time of injury should be discounted as it may not provide satisfactory protection against all antigens, and the scheduled immunisation should be given. Such additional doses are unlikely to produce an unacceptable rate of reactions (Ramsay *et al*., 1997).

Individuals aged ten years or over who have only had three doses of pertussis vaccine do not need further doses of pertussis-containing vaccine, except in pregnancy or as part of outbreak control (see below).

Pregnant women

Pregnant women should be offered a single dose of dTaP/IPV, ideally from 16 weeks to 32 weeks of pregnancy, although the vaccine can be offered after 32 weeks (For operational reasons, vaccination should be offered from around 20 weeks, on or after the foetal anomaly scan). This vaccine will act as a reinforcing dose and should be offered regardless of prior vaccination status, most adults having been primed by vaccination in infancy or by natural exposure during childhood.

Pertussis vaccine can be offered to pregnant women up until they go into labour. This is not the optimal time for immunisation however since antibody

levels in adults peak about two weeks after a pertussis booster. Vaccine administered between 16 to 32 weeks of pregnancy is likely to maximise the levels of pertussis antibodies transferred across the placenta, thereby providing passive immunity to the unborn child.

Immunisation after week 38 is unlikely to provide passive protection to the infant but would potentially protect the mother from pertussis infection and thereby reduce the risk of exposure to her infant. For women who have not received the vaccine in pregnancy, pertussis-containing vaccine can be offered in the two months following birth i.e. up until their child receives their first dose of pertussis-containing vaccine.

Vaccination of children with unknown or incomplete immunisation status

Where a child born in the UK presents with an inadequate immunisation history, every effort should be made to clarify what immunisations they may have had (see **Chapter 11**). A child who has not completed the primary course should have the outstanding doses at monthly intervals. Children may receive the first booster dose as early as one year after the third primary dose to re-establish them on the routine schedule.

Children coming to the UK who have a history of completing immunisation in their country of origin may not have been offered protection against all the antigens currently used in the UK. They will probably have received pertussis-containing vaccines in their country of origin:

http://apps.who.int/immunization_monitoring/globalsummary/schedules

Children coming from developing countries, from areas of conflict or from under-served population groups may not have been fully immunised. Where there is no reliable history of previous immunisation, it should be assumed that they are unimmunised, and the full UK recommendations should be followed (see **Chapter 11** on vaccine schedules).

Children coming to the UK may have had a fourth dose of a pertussis-containing vaccine that is given at around 18 months in some countries. This dose should be discounted as it may not provide satisfactory protection against tetanus, diphtheria and polio until the time of the teenage booster. The routine pre-school and subsequent boosters should be given according to the UK schedule.

Contraindications

There are very few individuals who cannot receive pertussis-containing vaccines. When there is doubt, appropriate advice should be sought from a consultant paediatrician, local Screening and Immunisation team or consultant in Health Protection rather than withhold vaccine.

The vaccines should not be given to those who have had:

- a confirmed anaphylactic reaction to a previous dose of a pertussis-containing vaccine, or
- a confirmed anaphylactic reaction to neomycin, streptomycin or polymyxin B (which may be present in trace amounts).

Confirmed anaphylaxis occurs extremely rarely. Data from the UK, Canada and the US point to rates of 0.65 to 3 anaphylaxis events per million doses of vaccine given (Bohlke *et al.,* 2003; Canadian Medical Association, 2002). Other allergic conditions may occur more commonly and are not contraindications to further immunisation. A careful history of the event will often distinguish between anaphylaxis and other events that are either not due to the vaccine or not life-threatening. In the latter circumstance, it may be possible to continue the immunisation course. Specialist advice must be sought on the vaccines and circumstances in which they could be given. The risk to the individual of not being immunised must be taken into account.

Precautions

Minor illnesses without fever or systemic upset are not valid reasons to postpone immunisation. If an individual is acutely unwell, immunisation should be postponed until they have fully recovered. This is to avoid confusing the differential diagnosis of any acute illness by wrongly attributing any signs or symptoms to the adverse effects of the vaccine.

Systemic and local reactions following a previous immunisation

This section gives advice on the immunisation of children with a history of a severe or mild systemic or local reaction within 72 hours of a preceding vaccine. Immunisation with pertussis-containing vaccine **should** continue following a history of:

- fever, irrespective of its severity
- hypotonic-hyporesponsive episodes (HHE)

- persistent crying or screaming for more than three hours
- severe local reaction, irrespective of extent.

Previous experience suggested that the above events occurred more often after whole-cell DTP vaccine than after DT alone or after DTaP. Following the replacement of whole-cell pertussis vaccine with an acellular pertussis vaccine (DTaP/IPV/Hib) in Canada, there was a significant reduction in the number of reports of febrile seizures collected through the Immunization Monitoring Program – ACTive (IMPACT) (Le Saux *et al.*, 2003). When DTaP vaccines were compared with DT alone, severe general and local reactions occurred at the same rate (Tozzi and Olin, 1997). Therefore, these reactions were not attributable to the acellular pertussis components.

Children who have had severe reactions, as above, have continued and completed immunisation with pertussis-containing vaccines without recurrence of these reactions (Vermeer-de Bondt *et al.*, 1998; Gold *et al.*, 2000).

In Canada, a severe general or local reaction to DTaP/IPV/Hib is not a contraindication to further doses of the vaccine (Canadian Medical Association, 1998). Adverse events after childhood immunisation are carefully monitored in Canada (Le Saux *et al.*, 2003), and experience there suggests that further doses are not associated with recurrence or worsening of the preceding events (S Halperin and R Pless, pers. comm., 2003).

Since local or general reactions are less frequent after acellular than whole-cell pertussis vaccines, the number of children with such events will be small. There is no benefit in withholding acellular pertussis-containing vaccines in order to reduce the risks of adverse events, and there is additional protection from completing pertussis immunisation; this should be carried out in accordance with the routine immunisation schedule. Children who have had a local or general reaction after whole-cell pertussis vaccine should complete their immunisation with acellular pertussis preparations.

Pregnancy and breast-feeding

Pertussis-containing vaccines should be given to pregnant women to protect their infants from birth. There is no evidence of risk from vaccinating pregnant women or those who are breast-feeding with inactivated viral or bacterial vaccines or toxoids (Kroger *et al.*, 2013).

Since the introduction of the maternal pertussis programme in October 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) has used the Yellow Card Scheme and the Clinical Practice Research Datalink to follow pregnancy outcomes following vaccination. The study based on a cohort of

18,000 vaccinated women showed that they had similar rates of normal, healthy births as unvaccinated women. The study also found no evidence of an increased risk of stillbirth and no evidence of an increased risk of any of an extensive list of adverse events related to pregnancy in vaccinated mothers (Donegan *et al*., 2014).

Premature infants

It is important that premature infants have their immunisations at the appropriate chronological age, according to the schedule. The occurrence of apnoea following vaccination is especially increased in infants who were born very prematurely.

Very premature infants (born ≤ 28 weeks of gestation) who are in hospital should have respiratory monitoring for 48-72 hrs when given their first immunisation, particularly those with a previous history of respiratory immaturity. If the premature infant has apnoea, bradycardia or desaturations after the first immunisation, the second immunisation should also be given in hospital, with respiratory monitoring for 48-72 hrs (Pfister *et al*., 2004; Ohlsson *et al*., 2004; Schulzke *et al*., 2005; Pourcyrous *et al*., 2007; Klein *et al*., 2008).

As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Immunosuppression and HIV infection

Individuals with immunosuppression and HIV infection (regardless of CD4 count) should be given pertussis-containing vaccines in accordance with the routine recommended schedule. These individuals may not make a full antibody response. Re-immunisation should be considered after treatment is finished and recovery has occurred. Specialist advice may be required.

Further guidance is provided by the Royal College of Paediatrics and Child Health (**http://www.rcpch.ac.uk/**), the British HIV Association (BHIVA) immunisation guidelines for HIV-infected adults (BHIVA, 2008; **http://www.bhiva.org/immunization-guidelines.aspx**) and the Children's HIV Association (CHIVA) immunisation guidelines (**http://www.chiva.org.uk/professionals/health/guidelines/index.html**).

Neurological conditions

Pre-existing neurological conditions

The presence of a neurological condition is not a contraindication to immunisation. Where there is evidence of a neurological condition in a child,

the advice given in the flow chart in Figure 24.4 should be followed.

If a child has a stable pre-existing neurological abnormality, such as spina bifida, congenital abnormality of the brain or perinatal hypoxic ischaemic encephalopathy, they should be immunised according to the recommended schedule. When there has been a documented history of cerebral damage in the neonatal period, immunisation should be carried out unless there is evidence of an evolving neurological abnormality

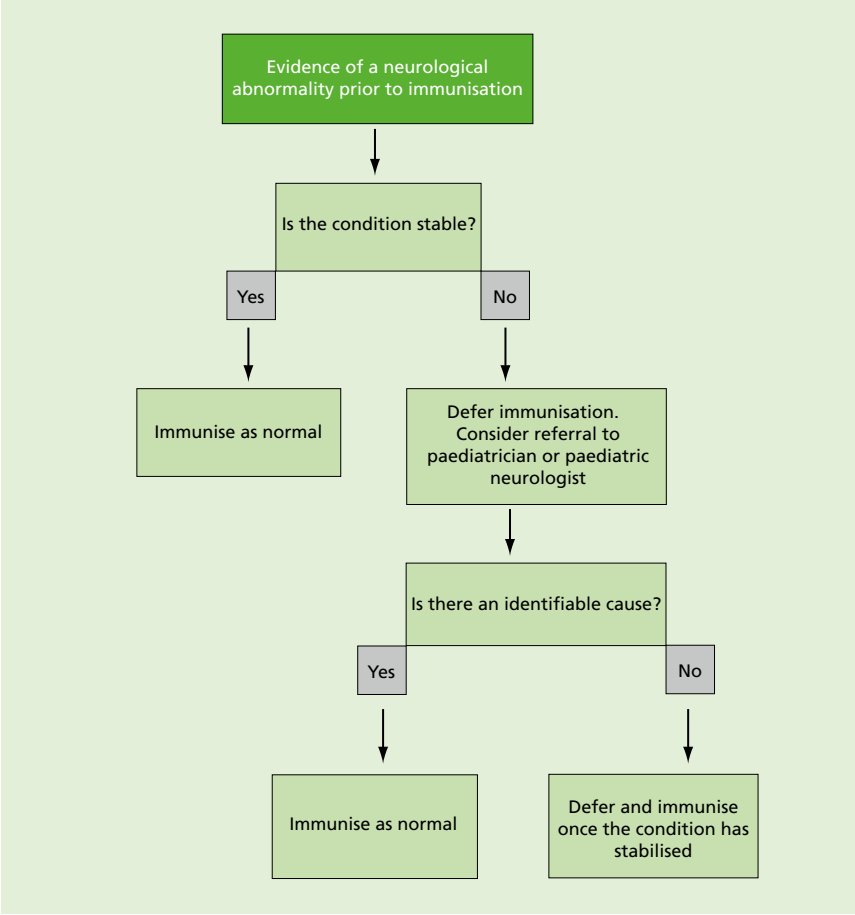

Figure 24.4 Flow chart for evidence of a neurological condition before immunisation

If there is evidence of current neurological deterioration, including poorly

controlled epilepsy, immunisation should be deferred and the child should be referred to a child specialist for investigation to see if an underlying cause can be identified. If a cause is not identified, immunisation should be deferred until the condition has stabilised. If a cause is identified, immunisation should proceed as normal.

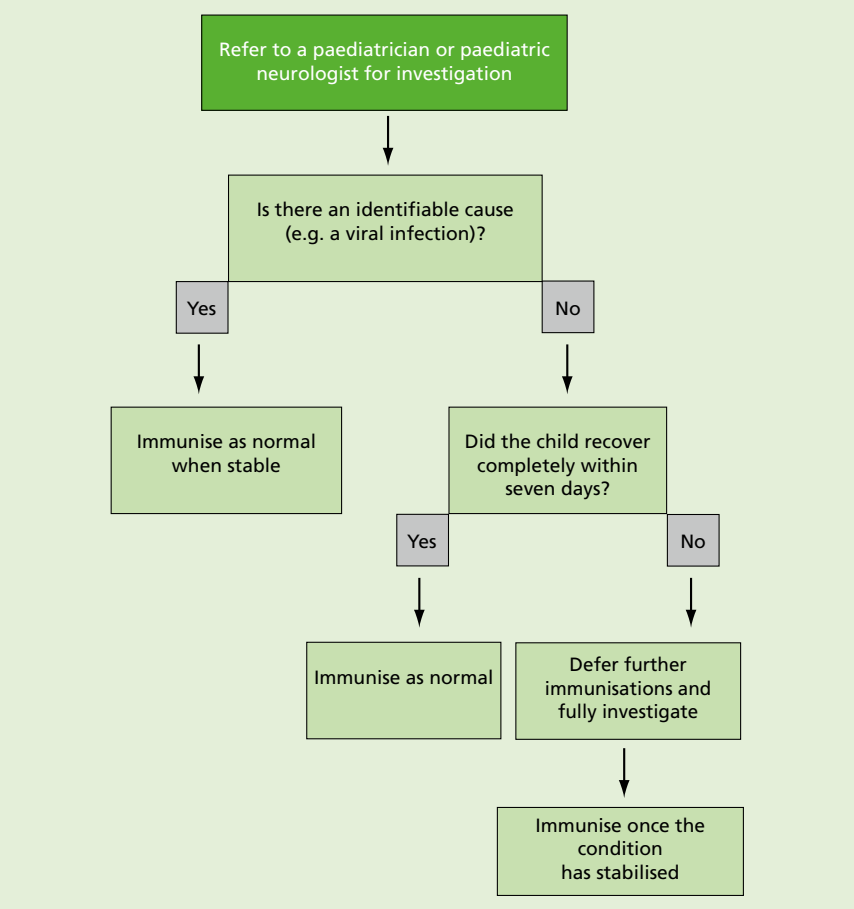

Figure 24.5 Flow chart for encephalitis or encephalopathy occurring within seven days of immunisation

A family history of seizures is not a contraindication to immunisation. When there is a personal or family history of febrile seizures, there is an increased risk of these occurring after any fever, including that caused by immunisation. Seizures associated with fever are rare in the first six months of life and most

common in the second year of life. After this age the frequency falls and they are rare after five years of age.

When a child has had a seizure associated with fever in the past, with no evidence of neurological deterioration, immunisation should proceed as recommended. Advice on the prevention and management of fever should be given before immunisation.

When a child has had a seizure that is not associated with fever, and there is no evidence of neurological deterioration, immunisation should proceed as recommended. When immunised with DTP vaccine, children with a family or personal history of seizures had no significant adverse events and their developmental progress was normal (Ramsay *et al.*, 1994).

Neurological abnormalities following immunisation

If a child experiences encephalopathy or encephalitis within seven days of immunisation, the advice in the flow chart in Figure 24.5 should be followed. It is unlikely that these conditions will have been caused by the vaccine and they should be investigated by a specialist. If a cause is identified or the child recovers within seven days, immunisation should proceed as recommended. In children where no underlying cause was found **and** the child did not recover completely within seven days, immunisation should be deferred until the condition has stabilised.

If a seizure associated with a fever occurs within 72 hours of an immunisation, immunisation should continue as recommended if a cause is identified or the child recovers within 24 hours. However, if no underlying cause has been found **and** the child did not recover completely within 24 hours, further immunisation should be deferred until the condition is stable.

Deferral of immunisation

There will be very few occasions when deferral of immunisation is required (see above). Deferral leaves the child unprotected; the period of deferral should be minimised so that immunisation can commence as soon as possible. If a specialist recommends deferral, this should be clearly communicated to the general practitioner, who must be informed as soon as the child is fit for immunisation.

Adverse reactions

Pain, swelling or redness at the injection site is common and may occur more frequently following subsequent doses. A small painless nodule may form

at the injection site; this usually disappears and is of no consequence. The incidence of local reactions is lower with vaccines combined with acellular pertussis than with whole-cell pertussis, and is similar to that after DT vaccine (Miller, 1999; Tozzi and Olin, 1997).

Fever, convulsions, high-pitched screaming and episodes of pallor, cyanosis and limpness (HHE) occur with equal frequency after both DTaP and DT vaccines (Tozzi and Olin, 1997).

Confirmed anaphylaxis occurs extremely rarely. Data from the UK, Canada and the US point to rates of 0.65 to 3 anaphylaxis events per million doses (Bohlke *et al.*, 2003; Canadian Medical Association, 2002). Other allergic conditions may occur more commonly and are not contraindications to further immunisation.

Anyone can report a suspected adverse reaction to the Medical and Healthcare products Regulatory Agency (MHRA) using the Yellow Card reporting scheme (**https://yellowcard.mhra.gov.uk/**). All suspected adverse reactions to vaccines occurring in children, or in individuals of any age after vaccination with vaccines labelled with a black triangle (▼), should be reported to the MHRA using the Yellow Card scheme. Serious suspected adverse reactions to vaccines in adults should be reported through the Yellow Card scheme.

Conditions historically associated with pertussis vaccine

In the past, there was public and professional anxiety that whole-cell pertussis vaccine contributed to the onset of neurological problems in young children; whole-cell pertussis vaccine has not been used in the UK since 2004. Between 1976 and 1979, a total of 1182 children with serious neurological illnesses were reported to the National Childhood Encephalopathy Study (NCES). Only 39 of these children had recently received whole-cell pertussis vaccine. The study concluded that whole-cell pertussis vaccine may very rarely be associated with the development of severe acute neurological illness in children who were previously apparently normal; most of these children suffered no long-term harm. The occurrence of a severe encephalopathy after whole-cell pertussis immunisation was sometimes associated with long-term residual neurological damage, but the evidence was insufficient to indicate whether or not whole-cell DTP increased the overall risk of chronic neurological dysfunction.

A major review of studies on adverse events after pertussis vaccine was published by the United States Institute of Medicine in 2001 (Howson *et al.,* 2001). This concluded that the evidence did not indicate a causal relationship between pertussis vaccine and infantile spasms, hypsarrhythmia, Reye's

syndrome and sudden infant death syndrome (SIDS).

Retrospective review of a small number of cases of encephalopathy in infants temporally associated with administration of pertussis-containing vaccines found that most had Dravet, or modified Dravet, syndrome, first recognised as 'severe myoclonic epilepsy of infancy' in 1978. Genetic analysis confirmed that most had mutations of the neuronal sodium channel gene *SCN1A* which is the major recognised cause of this syndrome. Thus, in many of the cases studied, the encephalopathy was of genetic origin (Berkovic *et al.,* 2006; McIntosh *et al.,* 2010).

Cot deaths (SIDS) occur most commonly during the first year of life and may therefore coincide with the giving of pertussis-containing vaccines. Studies have established that this association is not causal (Fleming *et al*., 2001).

It has been suggested that pertussis vaccine is linked with the development of asthma and allergy (Odent *et al*., 1994). A double-blind study of pertussis vaccines found no significant differences in wheezing, itchy rash or sneezing between DTP-immunised children and controls (Nilsson *et al*., 2003; DeStefano *et al*., 2002) and a birth cohort study showed no association between whole-cell pertussis vaccination in infancy and the development of asthma or allergy in later childhood (Maitra, 2004). Asthma or allergy are not contraindications to the completion of pertussis immunisation.

Management of outbreaks and contacts of cases

Antibiotic prophylaxis should be offered to all close contacts regardless of their immunisation status, where there is an unimmunised or partially immunised vulnerable close contact (*Guidelines for the public health management of pertussis*, October 2012).

https://www.gov.uk/government/publications/pertussis-guidelines-for-public-health-management

Cases should be reported and discussed with the local health protection team.

Immunisation should be considered for those who have been offered antibiotic prophylaxis. Further details are provided in *Guidelines for the public health management of pertussis*, October 2012.

Specific guidance on the management of pertussis incidents in healthcare settings and key public health actions can be found in *Pertussis: guidelines for public health management in a healthcare setting* (October 2012).

https://www.gov.uk/government/publications/pertussis-guidelines-for-public-health-management-in-a-healthcare-setting

Supplies

Some or all of the following vaccines containing pertussis antigens will be available at any one time:

- Pediacel®, diphtheria/tetanus/5-component acellular pertussis/inactivated polio vaccine/*Haemophilus influenzae* type b (DTaP/IPV/Hib) – manufactured by Sanofi Pasteur MSD.
- Repevax®, diphtheria/tetanus/5-component acellular pertussis/ inactivated polio vaccine (dTaP/IPV) – manufactured by Sanofi Pasteur MSD.
- Infanrix®-IPV,diphtheria/tetanus/3-componentacellularpertussis/inactivated polio vaccine (DTaP/IPV) – manufactured by GlaxoSmithKline.
- Boostrix®-IPV,diphtheria/tetanus/3-componentacellularpertussis/inactivated polio vaccine (dTaP/IPV) – manufactured by GlaxoSmithKline.
- Infanrix®-IPV+Hib, diphtheria/tetanus/3-component acellular pertussis/ inactivated polio vaccine/*Haemophilus influenzae* type b (DTaP/IPV/Hib) – manufactured by GlaxoSmithKline.

These vaccines are distributed by Movianto UK Ltd (Tel: 01234 248631) as part of the national childhood and prenatal immunisation programmes.

In Scotland, supplies should be obtained from local childhood vaccine holding centres. Details of these are available from Procurement, Commissioning & Facilities of NHS National Services Scotland (Tel: 0131 275 6725).

In Northern Ireland, supplies should be obtained from local childhood vaccine holding centres. Details of these are available from the Regional Pharmaceutical Procurement Service (Tel: 028 9442 4346).

References

American Academy of Pediatrics (2003) Active immunization. In: Pickering LK (ed.) *Red Book: 2003 Report of the Committee on Infectious Diseases* 26th edition. Elk Grove Village, IL: American Academy of Pediatrics, p 33.

Amirthalingam G, Andrews N, Campbell H *et al.* (2014) Effectiveness of maternal pertussis vaccination in England: an observational study. *Lancet* **384**(9953): 1521-28.

Amirthalingam G, Gupta S and Campbell H (2013) Pertussis immunisation and control in England and Wales, 1957 to 2012: a historical review. *Euro Surveill* **18**(38): pii: 20587.

Andrews N, Stowe J, Wise L *et al.* (2010) Post-licensure comparison of the safety profile of

diphtheria/tetanus/whole cell pertussis/haemophilus influenza type b vaccine and a 5-in-1 diphtheria/tetanus/acellular pertussis/haemophilus influenza type b/polio vaccine in the United Kingdom. *Vaccine* **28**(44): 7215-20.

Berkovic SF, Harkin L, McMahon JM *et al.* (2006) De-novo mutations of the sodium channel gene *SCN1A* in alleged vaccine encephalopathy: a retrospective study. *Lancet Neurol* **5**(6): 488-92.

BHIVA (2008) British HIV Association guidelines for immunization of HIV-infected adults 2008. *HIV Med* **9**(10): 795-848. **http://www.bhiva.org/documents/Guidelines/Immunisation/Immunization2008.pdf**. Accessed March 2015.

Bohlke K, Davis RL, Marcy SM *et al.* (2003) Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics* **112**(4): 815–20.

Campbell H, Amirthalingam G, Andrews N *et al.* (2012) Accelerating control of pertussis in England and Wales. *Emerg Infect Dis* **18**(1): 38-47.

Campbell H, Amirthalingam G, Fry NK *et al.* (2014) Oral fluid testing for pertussis, England and Wales, June 2007-August 2009. *Emerg Infect Dis* **20**(6): 968-75.

Canadian Medical Association (1998) Pertussis vaccine. In: *Canadian Immunisation Guide*, 5th edition. Canadian Medical Association, p 133.

Canadian Medical Association (2002) General considerations. In: *Canadian Immunisation Guide*, 6th edition. Canadian Medical Association, p 14.

Cherry JD (2012) Epidemic pertussis in 2012 - the resurgence of a vaccine-preventable disease. *N Engl J Med* **367**(9): 785-7.

Crowcroft NS, Andrews N, Rooney C *et al.* (2002) Deaths from pertussis are underestimated in England. *Arch Dis Child* **86**(5): 336–8.

Crowcroft NS, Booy R, Harrison T *et al.* (2003) Severe and unrecognised: pertussis in UK infants. *Arch Dis Child* **88**(9): 802–6.

Dabrera G, Amirthalingam G, Andrews N *et al.* (2014) Case-Control Study to Estimate the Effectiveness of Maternal Pertussis Vaccination in Protecting Newborn Infants in England and Wales, 2012-2013. *Clin Infect Dis* doi:10.1093/cid/ciu821. Available at:

http://cid.oxfordjournals.org/content/early/2014/11/17/cid.ciu821.long. Accessed March 2015.

Department of Health (2013) *Health Technical Memorandum 07-01: Safe management of healthcare waste.* **https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/167976/HTM_07-01_Final.pdf**. Accessed March 2015.

DeStefano F, Gu D, Kramarz P *et al.* (2002) Childhood vaccinations and risk of asthma. *Pediatr Infect Dis J* **21**(6): 498–504.

Diggle L and Deeks J (2000) Effect of needle length on incidence of local reactions to routine immunisation in infants aged 4 months: randomised controlled trial. *BMJ* **321**(7266): 931–3.

Donegan K, King B and Bryan P (2014) Safety of pertussis vaccination in pregnant women in UK: observational study. *BMJ* 349:g4219. Available at **http://www.bmj.com/content/bmj/349/bmj.g4219.full.pdf**. Accessed March 2015.

Eberhardt C, Blanchard-Rohner G, Lemaitre B *et al*. (2016) Maternal Immunization earlier in pregnancy maximises maternal antibody transfer and expected infant seropositivity against pertussis. *Clin Infect Dis* **62**(7): 829-836.

Edwards KM and Decker MD (2013) Pertussis vaccines. In: Plotkin SA, Orenstein WA and Offit PA (eds). *Vaccines*, 6th edition. Philadelphia: Saunders, Elsevier, p 447.

Fleming PJ, Blair PS, Platt MW *et al*. (2001) The UK accelerated immunisation programme and sudden unexpected death in infancy: case-control study. *BMJ* **322**(7290): 1–5.

Gold M, Goodwin H, Botham S *et al*. (2000) Re-vaccination of 421 children with a past history of an adverse vaccine reaction in a special immunisation service. *Arch Dis Child* **83**: 128–31.

Howson CP, Howe CJ and Fineberg HV (eds) (2001) *Adverse effects of pertussis and rubella vaccines. A report of the committee to review the adverse consequences of pertussis and rubella vaccines.* Institute of Medicine Report. Washington, DC: National Academy Press.

Joint Committee on Vaccination and Immunisation: Minute of the meeting held on 3 February 2016. **https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation**

Klein NP, Massolo ML, Greene J *et al*. (2008) Risk factors for developing apnea after immunization in the neonatal intensive care unit. *Pediatrics* **121**(3): 463-9.

Kroger AT, Atkinson WL and Pickering LK (2013) General immunization practices. In: Plotkin SA, Orenstein WA and Offit PA (eds). *Vaccines*, 6th edition. Philadelphia: Saunders Elsevier, p 88.

Le Saux N, Barrowman NJ, Moore DL *et al*. for members of the Canadian Paediatric Society/Health Canada Immunization Monitoring Program–Active (IMPACT) (2003) Decrease in hospital admissions for febrile seizures and reports of hypotonic-hyporesponsive episodes presenting to hospital emergency departments since switching to acellular pertussis vaccine in Canada: a report from IMPACT. *Pediatrics* **112**(5): e348.

Maitra A, Sherriff A, Griffiths M, Henderson J; Avon Longitudinal Study of Parents and Children Study Team (2004) Pertussis vaccination in infancy and asthma or allergy in

later childhood: birth cohort study. *BMJ* **328**(7445): 925-6.

Mark A, Carlsson RM and Granstrom M (1999) Subcutaneous versus intramuscular injection for booster DT vaccination of adolescents. *Vaccine* **17**(15-16): 2067–72.

McIntosh AM, McMahon J, Dibbens LM *et al.* (2010) Effects of vaccination on onset and outcome of Dravet syndrome: a retrospective study. *Lancet Neurol* **9**(6): 592-8.

Miller E (1999) Overview of recent clinical trials of acellular pertussis vaccines. *Biologicals* **27**(2): 79–86.

Miller CL and Fletcher WB (1976) Severity of notified whooping cough. *BMJ* **1**(6002): 117–19.

Nilsson L, Kjellman NI and Bjorksten B (2003) Allergic disease at the age of 7 years after pertussis vaccination in infancy: results from the follow-up of a randomised controlled trial of 3 vaccines. *Arch Pediatr Adolesc Med* **157**(12): 1184–9.

Odent MR, Culpin EE and Kimmel T (1994) Pertussis vaccination and asthma: is there a link? *JAMA* **272**(8): 592–3.

Ohlsson A and Lacy JB (2004) Intravenous immunoglobulin for preventing infection in preterm and/or low-birth-weight infants. *Cochrane Database Syst Rev* (1): CD000361.

Pfister RE, Aeschbach V, Niksic-Stuber V *et al.* (2004) Safety of DTaP-based combined immunization in very-low-birth-weight premature infants: frequent but mostly benign cardiorespiratory events. *J Pediatr* **145**(1): 58-66.

Pourcyrous M, Korones SB, Arheart KL *et al.* (2007) Primary immunization of premature infants with gestational age <35 weeks: cardiorespiratory complications and C-reactive protein responses associated with administration of single and multiple separate vaccines simultaneously. *J Pediatr* **151**(2): 167-72.

Public Health England (2014). Laboratory confirmed pertussis in England: data to end-October 2014. *Health Protection Report* **8**(47). **https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/388854/hpr4714_prtsss.pdf.** Accessed March 2015.

Ramsay M, Begg N, Holland B *et al.* (1994) Pertussis immunisation in children with a family or personal history of convulsions: a review of children referred for specialist advice. *Health Trends* **26**(1): 23–4.

Ramsay M, Joce R and Whalley J (1997) Adverse events after school leavers received combined tetanus and low-dose diphtheria vaccine. *Commun Dis Rep CDR Rev* **7**(5): R65–7.

Schulzke S, Heininger U, Lucking-Famira M *et al.* (2005) Apnoea and bradycardia in

preterm infants following immunisation with pentavalent or hexavalent vaccines. *Eur J Pediatr* **164**(7): 432-5.

Summary of Product Characteristics, Infanrix®-IPV+Hib. **https://www.medicines.org.uk/emc/medicine/28678**. Accessed March 2015.

Tozzi AE and Olin P (1997) Common side effects in the Italian and Stockholm I trials. *Dev Biol Stand* **89**: 105–8.

van Hoek AJ, Andrews N, Campbell H *et al*. (2013a) The social life of infants in the context of infectious disease transmission; social contacts and mixing patterns of the very young. *PLoS One* **8**(10): e76180.

van Hoek AJ, Campbell H, Amirthalingam G *et al*. (2013b) The number of deaths among infants under one year of age in England with pertussis: results of a capture/recapture analysis for the period 2001 to 2011. *Euro Surveill* **18**(9): pii: 20414.

Vermeer-de Bondt PE, Labadie J and Rümke HC (1998) Rate of recurrent collapse after vaccination with whole cell pertussis vaccine: follow up study. *BMJ* **316**(7135): 902-3.

World Health Organization (2010) Pertussis vaccines: WHO position paper. *Wkly Epidemiol Rec* **85**(40): 385-400.

Zuckerman JN (2000) The importance of injecting vaccines into muscle. Different patients need different needle sizes. *BMJ* **321**(7271): 1237–8.