



Public Health
England

Protecting and improving the nation's health

The hexavalent DTaP/IPV/Hib/HepB combination vaccine

Information for healthcare practitioners about the inclusion of hepatitis B vaccine in the **routine** infant immunisation programme

About Public Health England

Public Health England's mission is to protect and improve the nation's health and to address inequalities through working with national and local government, the NHS, industry and the voluntary and community sector. PHE is an operationally autonomous executive agency of the Department of Health.

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Background

From autumn 2017, all babies born on or after 1 August 2017 will be eligible for a hexavalent vaccine which includes hepatitis B (HepB) for their primary immunisations. This vaccine, called Infanrix hexa®, will replace the pentavalent infant vaccines Infanrix®-IPV+Hib and Pediacel®. The following questions and answers are intended to provide healthcare professionals with more information about this vaccine.

Healthcare professionals with a responsibility for vaccinating babies at risk of hepatitis B (i.e. those born to mothers infected with hepatitis B virus) may find the answers to questions about these babies in '*The hexavalent DTaP/IPV/Hib/HepB combination vaccine: Information for healthcare practitioners about the neonatal selective immunisation programme for babies at risk of hepatitis B*' available on the PHE Immunisation webpages.

Infanrix hexa® vaccine

Infanrix hexa® is a combination vaccine used for primary vaccination of infants to protect against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and disease caused by *Haemophilus influenzae* type b. Infanrix hexa® can also be used for catch-up immunisation for children up to their 10th birthday where these children have missed out on doses of primary immunisations. Multiple studies have shown Infanrix hexa® to be safe and highly immunogenic for all its component toxoids/antigens¹.

When Infanrix hexa® will be introduced into the infant schedule

All babies born on or after 1st August 2017 will become eligible for the vaccine eight weeks after their birth. Infanrix hexa® vaccine is expected to be made available to order online through the ImmForm website (www.immform.dh.gov.uk) from 1st September 2017 and will be distributed by Movianto UK for use in the routine childhood primary immunisation schedule at 8, 12 and 16 weeks of age.

Infants born before 1st August 2017 should complete the course with pentavalent vaccine (Pediacel® or Infanrix-IPV+Hib®). Infanrix hexa® should only be given to babies born before 1st August if there is no locally held vaccine stock and no further Pediacel® or Infanrix-IPV+Hib® can be ordered through ImmForm. It should also be given if pentavalent vaccine is not readily available - vaccination should never be delayed in order to obtain the pentavalent vaccine.

¹ Dhillion S. DTPa-HBV-IPV/Hib vaccine (Infanrix hexa™) A Review of its Use as a Primary and Booster Vaccination. Drugs 2010; 70(8): 1021-1058 Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20481658>

Why Infanrix hexa® is being introduced into the infant schedule

Hepatitis B is an infection of the liver caused by the hepatitis B virus (HBV). Most new infections with HBV are sub-clinical or may only cause a flu-like illness. However, acute infection occasionally leads to sudden and severe liver damage which can be fatal. Chronic HBV infection can result in progressive liver disease, leading to cirrhosis (development of scar tissue) in some patients and an increased risk of developing liver cancer.

In 1992, the World Health Assembly recommended that every country should have a universal hepatitis B immunisation programme by 1997². As the UK is a low prevalence and low incidence country for hepatitis B however, introducing a universal hepatitis B programme using a monovalent hepatitis B vaccine would not have been cost-effective. Recently, infant combination hepatitis B vaccines (which also protect against diphtheria, tetanus, polio, pertussis and Hib) have become available in the UK. In 2014, therefore, the Joint Committee of Vaccination and Immunisation (JCVI) re-evaluated the benefits and cost-effectiveness of a universal hepatitis B infant immunisation programme in the UK and subsequently recommended the use of the hexavalent DTaP/IPV/Hib/HepB combination vaccine for all infants subject to securing the vaccine at a cost-effective price.

By providing hepatitis B vaccine as part of the combined infant vaccine, as well as being protected against diphtheria, tetanus, pertussis, polio and Hib, infants will now have the benefit of protection against hepatitis B virus.

Other countries where Infanrix hexa® is used

Infanrix hexa® is not a new vaccine. It is licensed for use in 97 other countries across the world including Canada, Australia and New Zealand. The vaccine was first licensed for use in Europe in October 2000 and approximately 150 million doses have been given to infants in Europe and across the world.

The difference between Infanrix hexa®, Infanrix®-IPV+Hib and Pediacel®

All of these vaccines protect against the same five diseases (tetanus, diphtheria, whooping cough, polio and Hib). The main difference is that Infanrix hexa® also offers protection against hepatitis B.

² World Health Organization, Immunization, Vaccines and Biologicals. Hepatitis B. [internet] accessed 28 June 2017. Available at: http://www.who.int/immunization/topics/hepatitis_b/en/

Two other differences between these products are that:

1. Infanrix hexa® and Infanrix®-IPV+Hib vaccine contain three pertussis components while Pediacel® has five components but with slightly lower antigen content.
2. Infanrix hexa® and Infanrix®-IPV+Hib require reconstitution before being administered. Pediacel® is presented in a pre-filled syringe.

Safety and efficacy of Infanrix hexa® vaccine

The safety profile of Infanrix hexa® is excellent. Any adverse events experienced are mild to moderate and are similar to those experienced following administration of the Pediacel® and Infanrix®-IPV+Hib vaccines¹. These may include redness, swelling and tenderness at the injection site, fever, irritability, loss of appetite, diarrhoea and vomiting³.

Results from clinical trials show that nearly all infants given the three dose primary vaccination course of Infanrix hexa® at two, three and four months of age develop protective levels of antibodies against diphtheria (100%), tetanus (100%), pertussis (100%), hepatitis B (99.5%), polio (98-100%) and Hib (96%)³.

Vaccine scheduling

The schedule for Infanrix hexa®

The infant immunisation schedule remains unchanged at eight, twelve and sixteen weeks of age. The minimum age for a first dose is six weeks of age.

The first dose of Infanrix hexa® can be given from six weeks if required in certain circumstances e.g. travel to an endemic country. Rotavirus, MenB and the pneumococcal conjugate vaccine (PCV) should also be given at the same time. The schedule should then be completed with a minimum of four weeks between subsequent doses of Infanrix hexa® and eight weeks between subsequent doses of MenB and PCV.

³ Infanrix hexa Summary of Product Characteristics. [internet] accessed 28 June 2017. Available at: <https://www.medicines.org.uk/emc/medicine/33313>

Administration of Infanrix hexa® with other infant vaccines

Infanrix hexa® can be administered at the same time as, or at any time before or after any other vaccine. Other countries routinely offer Infanrix hexa® with the other infant vaccines, including rotavirus, pneumococcal conjugate vaccine and MenB.

Giving Infanrix hexa® to premature infants

Clinical data indicate that Infanrix hexa® can be given to premature infants and it is important that premature infants receive their immunisations at the appropriate chronological age (i.e. age since birth, not corrected), according to the schedule. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

In comparative clinical studies, similar rates of adverse reactions were observed in pre-term and full-term infants. However, as for pentavalent vaccines, the occurrence of apnoea following vaccination is increased in infants who were born very prematurely. Very premature infants (born \leq 28 weeks of gestation) who are in hospital should have respiratory monitoring for 48 to 72 hours when given their first immunisation, particularly those with a previous history of respiratory immaturity. If the child has apnoea, bradycardia or desaturations after the first immunisation, the second immunisation should also be given in hospital, with respiratory monitoring for 48 to 72 hours.

What you should do if the vaccine course is interrupted or an infant misses a scheduled dose

If the primary course of Infanrix hexa® is interrupted, it should be resumed but not repeated, allowing an interval of four weeks between the remaining doses. Missed doses should be given as soon as possible.

What you should give children with incomplete, uncertain or non-UK primary immunisations

If the child was born before 1st August 2017 in the UK or abroad and started on pentavalent vaccine, they should complete the primary course with pentavalent vaccine. Where possible, it is preferable that the same DTaP/IPV/Hib vaccine should be used for all three doses of the primary course. If a different pentavalent vaccine is available from the one given to the child previously however, this other pentavalent vaccine should be given.

If a pentavalent vaccine is no longer or not readily available, give hexavalent vaccine. This will provide equivalent protection against diphtheria, tetanus, pertussis, polio and

Hib but the child will not be fully protected against hepatitis B. This is not a concern unless the child is at risk of hepatitis B (in which case a course of hepatitis B-containing vaccine should be given).

Vaccination should never be delayed in order to obtain pentavalent vaccine.

If the child was born abroad before 1st August 2017 and started on hexavalent vaccine in their country of origin they should complete their primary course with hexavalent vaccine. It is good practice to complete a course with the vaccine given previously where possible and it may be that hepatitis B is included in the primary schedule of their country of origin because there is a higher prevalence of hepatitis B.

If the child was born abroad after 1st August 2017 and started on pentavalent vaccine, they should complete the course with the hexavalent vaccine. Additional doses of monovalent hepatitis B vaccine to complete a three dose hepatitis B course should only be given if they have specific risk indications.

If the child was born abroad after 1st August 2017 and received three doses of pentavalent vaccine for their complete primary course, they should only receive monovalent hepatitis B vaccine if there is a specific indication to do so e.g. if the child will be regularly returning to a country with high prevalence of hepatitis B infection.

Booster and catch-up doses

No catch up programme for babies born before 1st August 2017

When any new vaccine programme is introduced, there always has to be a cut-off for eligibility. The incidence of hepatitis B is currently low in children and by vaccinating all infants born on or after 1 August 2017, this will ultimately help to keep the incidence of HBV low in the population as a whole. Any individuals born before 1st August 2017, will, as always, be eligible for hepatitis B vaccine if they are identified as being at increased risk of HBV.

Infants given the hexavalent hepatitis B-containing vaccine do not need a booster dose of hepatitis B vaccine

For infants who have completed a primary course of vaccination, a routine booster dose of vaccine is not required (except for high risk infants who should receive an additional dose of monovalent Hepatitis B vaccine at 12 months of age).

The full duration of protection afforded by hepatitis B vaccine is expected to be greater than 20 years. Even though levels of vaccine-induced antibody to hepatitis B decline over time, there is evidence that immune memory persists in those successfully immunised. If they are exposed later in life, this immune memory will help to protect them against serious disease and chronic infection. If there is a significant exposure to an unknown or known hepatitis B surface antigen (HBsAg) positive source however, a booster dose of vaccine may be indicated.

For those who may become at risk of infection later in life, for example if they become health care workers, additional doses of vaccine and/or antibody testing may be required – check the [Green Book Hepatitis B chapter](#).

Contraindications

Contraindications to Infanrix hexa®

Infanrix hexa® should not be administered to those who have had:

1. A confirmed anaphylactic reaction to a previous dose of the vaccine OR
2. A confirmed anaphylactic reaction to any component of the vaccine (this includes formaldehyde, neomycin and polymyxin).

There are very few individuals who cannot receive the Infanrix hexa® vaccine. Where there is doubt, instead of withholding immunisation, appropriate advice should be sought from a consultant with immunisation expertise or a member of the local Screening and Immunisation or Health Protection team.

Precautions to Infanrix hexa®

As for pentavalent vaccine, there are very few occasions when deferral of immunisation with Infanrix hexa® is required.

If an infant has a minor illness without fever or systemic upset, immunisations can still be given. If the infant is acutely unwell (for example with a fever above 38.5°C), immunisation may be postponed until they have fully recovered. This is to avoid wrongly attributing any new symptom or the progression of symptoms to the vaccine.

The presence of a neurological condition is not a contraindication to immunisation but if there is evidence of current neurological deterioration, deferral of the DTaP/IPV/Hib/HepB vaccine may be considered to avoid incorrect attribution of any change in the underlying condition. The risk of such deferral should be balanced

against the risk of the preventable infection and vaccination should be promptly given once the diagnosis and/or the expected course of the condition becomes clear.

Children who have had a systemic or local reaction following a previous immunisation with DTaP/IPV/Hib/HepB or DTaP/IPV/Hib including:

- fever, irrespective of its severity
- hypotonic-hyporesponsive episodes (HHE)
- persistent crying or screaming for more than three hours, or
- severe local reaction, irrespective of extent

can continue to receive subsequent doses of DTaP/IPV/Hib/HepB vaccine. Seek further advice if required.

Very premature infants (born \leq 28 weeks of gestation) who are in hospital should have respiratory monitoring for 48-72 hrs when given their first immunisation (see section on premature infants above).

Vaccine storage and administration

Storage of Infanrix hexa®

Infanrix hexa® should be stored between +2°C to +8°C and protected from light. Do not freeze. Infanrix hexa® must be stored in its original packaging to protect it from light, to ensure that the component parts are kept together and in order to retain the batch number and expiry date for the entire product which is printed on the outer vaccine carton.

In the event of an inadvertent or temporary temperature excursion outside of the recommended +2°C to +8°C range, stability data detailed in the [Summary of Product Characteristics](#) indicate that the vaccine components are stable at temperatures up to 25°C for 72 hours. Breaches in the cold chain should be reported to the Screening and Immunisation Team in line with local arrangements but Infanrix hexa® that has not exceeded 8°C for more than 72 hours nor exceeded 25°C may be used.

Vaccine that has exceeded 25°C or been exposed to temperatures above 8°C for more than 72 hours should be quarantined and further advice should be sought from the local Screening and Immunisation or Health Protection Team.

Infanrix hexa® presentation

- The vaccine is presented in two parts and it is very important that the freeze dried Hib component is reconstituted correctly before administration
- The DTaP/IPV/HepB component is presented as a cloudy white suspension in a pre-filled glass syringe. Upon storage, a clear liquid and a white deposit may be observed. This is a normal observation.
- The freeze dried (lyophilised) Hib vaccine is presented as a white powder in a glass vial.
- The Infanrix hexa® vaccine is supplied in single dose packs containing the syringe, vial and two needles – one for reconstitution and one for vaccine administration.

Preparation of Infanrix hexa®

1. Shake the pre-filled syringe containing the DTaP/IPV/HepB suspension in order to obtain a consistent, cloudy, white suspension.
2. Attach the green needle supplied to the pre-filled syringe of DTaP/IPV/HepB and inject the entire contents of the syringe into the vial containing the Hib vaccine (as a powder).
3. Shake the vial vigorously until the powder has completely dissolved.
4. Withdraw the entire mixture back into the syringe.
5. The reconstituted vaccine appears as a slightly more cloudy suspension than the liquid component alone. This is a normal observation.
6. Inspect the vaccine suspension for any foreign particulate matter and/or abnormal physical appearance. If either is observed, discard the vaccine.
7. Replace the green needle with the blue needle supplied and administer the vaccine intramuscularly.

Adminstration

Infanrix hexa® should be administered intramuscularly to all infants with the exception of those with a bleeding disorder who should receive the vaccine by deep subcutaneous injection to reduce the risk of bleeding.

The preferred site of injection for infants under one year of age is the anterolateral aspect of the thigh. As Infanrix hexa® is not a new vaccine (it has been given in many other countries for a number of years), it does not need to be given on its own so should preferably be given in the same thigh (right thigh) as the pneumococcal conjugate vaccine (PCV) at the 8 week and 16 week immunisation appointments. Although it is recommended that MenB, as the newest vaccine, is given on its own into the left thigh, it does not matter if MenB vaccine and Infanrix hexa® are inadvertently given into the same thigh.

When two vaccines are given in the same limb, they should be given at least 2.5cm apart and the site at which each vaccine was given should be noted in the individual's records.

Post-immunisation care recommendations

The recommendations following administration of Infanrix hexa® vaccine are the same as with the administration of Pediacel® and Infanrix®-IPV+Hib vaccines.

When PCV is given alongside infant DTaP-containing combination vaccines, the rate of fever is higher than when either vaccine is administered alone. In the current UK schedule, infants receive these vaccines alongside MenB vaccination at 8 and 16 weeks of age. The routine recommendation to offer prophylactic paracetamol with the infant doses of MenB is expected to also reduce the rate of fever attributed to co-administration of PCV.

For further information about administration of paracetamol, please see [MenB vaccine and paracetamol](#) webpage and the “[What to expect after vaccinations](#)” leaflet on the [PHE Immunisation](#) webpage.

What you should do with remaining stocks of the pentavalent DTaP/IPV/Hib vaccine

The Infanrix hexa® vaccine is expected to be made available to order through ImmForm from 1 September 2017 in readiness for the planned switch over from late September/early October 2017. Up to this changeover date, to avoid potential wastage, you should aim to run down the volume of Pediacel® and Infanrix-IPV+Hib® vaccines held in stock and only order the minimum volume to complete vaccination of babies born before August. Infanrix hexa® should only be given to older babies (i.e. born before 1 August) if there is no locally held vaccine stock, no further Pediacel® or Infanrix-IPV+Hib® can be ordered through ImmForm or no pentavalent vaccine is readily available. Further details and any amendments to this date or arrangements will be provided through future issues of [Vaccine Update](#).

Following the introduction of Infanrix hexa® for babies born on or after 1 August, in order to avoid any wastage of the existing vaccines used for this programme, any remaining stocks of Pediacel® and Infanrix-IPV+Hib® (DTaP/IPV+Hib) should be used for babies who have already started courses with Pediacel® or Infanrix-IPV+Hib® (second or third dose), or if vaccine still remains, then as a temporary measure, this can be used for pre-school boosting at the age of 3 years and 4 months. Once these stocks are used up, pre-school boosting should revert back to Repevax® (dTaP/IPV).

Potential vaccine errors

What you should do if a dose of Infanrix hexa® is given at an interval of less than four weeks in error

As for pentavalent vaccine, a four week interval is recommended between each of the three doses of Infanrix hexa® vaccine in the primary schedule. If one of these doses is given up to a week early, either inadvertently or deliberately e.g. for travel reasons, then this can be counted as a valid dose and does not need to be repeated. However, no more than one dose should be given early in the three dose schedule and any doses given at less than a three week interval should be repeated four weeks after the dose given early.

Actions to take if the immuniser forgets to reconstitute the Hib component of the vaccine and only administers the DTaP/IPV/HepB component

A dose of the combined Hib/MenC vaccine (Menitorix) should be given either at the same visit or as soon as possible after the error is realised in order to provide protection against Hib.

All vaccine errors should be reported to the local Screening and Immunisation Team. It is important to establish if the error was a one-off occurrence or a systematic error that might require a look back exercise.

What to do if the pentavalent DTaP/IPV/Hib vaccine is given in error to an infant who is eligible to receive the hexavalent DTaP/IPV/Hib/HepB vaccine

If the infant is at immediate high risk, give a dose of monovalent hepatitis B vaccine as soon as the error is realised. Otherwise, the infant should complete the primary course with hexavalent vaccine and an additional dose of hexavalent vaccine should then be given at least four weeks after completion of the primary course. If more than one dose of hexavalent vaccine is missed in the primary schedule, give Infanrix hexa® at the pre-school visit.

What to do if Infanrix hexa® is inadvertently given as a pre-school booster vaccine

If Infanrix hexa® is inadvertently given to children as a pre-school booster instead of the recommended Infanrix-IPV® or Repevax® vaccines, this is not a clinical safety issue and the vaccine will still boost their antibodies against diphtheria, tetanus,

pertussis and polio as the recommended pre-school booster vaccine would have done. From a supply viewpoint however, efforts should be made to use the correct vaccine.

Vaccine composition

Composition of Infanrix hexa® vaccine

As well as the diphtheria, tetanus, pertussis, polio, Hib and Hepatitis B antigens, Infanrix hexa® vaccine also contains the following:

The vial containing Hib powder also contains:

- Lactose anhydrous

The pre-filled syringe containing the DTaP/IPV/HepB suspension also contains:

- Sodium chloride
- Medium 199 containing principally amino acids, mineral salts, vitamins
- Water for injections

The vaccine contains the following adjuvants (substances added to enhance the immune response to the antigens):

- Aluminium hydroxide, hydrated
- Aluminium phosphate

The vaccine may also contain traces of formaldehyde, neomycin and polymyxin which are used during the manufacturing process for inactivation and prevention of bacterial growth.

The composition of the vaccine and excipients (other substances contained in the vaccine besides the DTaP/IPV/Hib/HepB antigens) are listed in the vaccine manufacturer's [Summary of Product Characteristics \(SPC\)](#).

Infanrix hexa® does not contain any thiomersal or porcine gelatine.

Addressing parental concerns

What to say to a parent who is worried about having a new vaccine

Firstly, Infanrix hexa® is not a new vaccine. It is licensed for use in 97 other countries across the world including Canada, Australia and New Zealand. Since the vaccine was licensed for use in October 2000, approximately 150 million doses have been safely and effectively given to infants across the world with no evidence of harmful effects.

Secondly, by combining DTaP/IPV/Hib and HepB, infants can be provided with protection against six harmful diseases at the very earliest opportunity in a single injection. The five-in-one DTaP/IPV/Hib vaccine has been given to infants in the UK since 2004 and is highly efficacious and well tolerated. The hepatitis B vaccine has been used since 1981 and is also well-tolerated and highly efficacious. Numerous studies have shown that the hepatitis B vaccine can be added to the DTaP/IPV/Hib vaccine without affecting the protective response made to all the component parts or the frequency or type of adverse reactions experienced¹.

What to say to a parent who is concerned about receiving a vaccine containing six components

It is acknowledged that some parents may be concerned that their child is receiving a six component combination vaccine. Whilst these concerns are understandable, parents should be reassured that there is no evidence to support arguments of “overloading” the immune system. From the moment a child is born, they are continually being exposed to a huge number of bacteria and viruses on a daily basis. From birth, their immune system is able to respond to both the many antigens in the environment and the relatively small number of selected antigens in vaccines⁴.

Additionally, before a combined vaccine is licensed for use, it must have demonstrated in pre-licensure studies that a satisfactory immune response is made to each of the combined antigens and that the rates of adverse reactions are lower or the same as they would be if the vaccines were administered separately.

What to do if a parent does not want to receive a vaccine containing hepatitis B

Healthcare professionals should ascertain what the parent’s specific concerns about the Infanrix hexa® vaccine are and address these. They should also provide them with information as to the benefits of receiving this hexavalent vaccine.

As the pentavalent vaccine is being phased out and will shortly be unavailable, there will be no alternative vaccine with which to adequately protect infants and children against diphtheria, tetanus, polio, pertussis and Hib disease. The vaccines that are licensed for pre-school boosters contain lower levels of antigens and are therefore only suitable for boosting children who have already received infant vaccination.

⁴ Centre for Disease Control (CDC). Multiple Vaccinations and the Immune System. [internet] accessed 28 June 2017. <http://www.cdc.gov/vaccinesafety/Vaccines/multiplevaccines.html>

Other issues

Protection against whooping cough from three component acellular pertussis (3aP) vaccines compared to five component (5aP) vaccines

Between 2004 and 2008, the UK only used infant acellular pertussis vaccines that contained five components to ensure optimal protection against whooping cough. UK follow up of children who had received a 3aP vaccine suggested, however, that protection was equivalent to 5aP vaccines to pre-school age⁵. In 2008, JCVI advised that a 3aP combination vaccine could be used for primary immunisation. In 2010, the WHO also reviewed all the global data on pertussis control in countries using acellular vaccines⁶. They concluded that acellular pertussis vaccines with three or more components have higher protective efficacy than vaccines with fewer components and did not find consistent evidence of a difference between three and five components. A 3aP component vaccine (Infanrix®-IPV+Hib), similar to Infanrix hexa®, has now been used widely in the UK since 2014.

Hib antibody response to the Infanrix hexa® vaccine

Between 2004 and 2008, the UK only used infant acellular pertussis vaccines that contained five components to ensure optimal protection against Hib. This was because there had been concern that the available infant combination vaccines (those including a 3-component acellular-pertussis vaccine) could produce an inferior response to Hib. A 3aP component vaccine (Infanrix®-IPV+Hib), similar to Infanrix hexa®, has now been used widely in the UK since 2014. Experience suggests that with the current UK schedule of 3 doses in infancy and a Hib booster at one year of age, adequate protection will be achieved and control of Hib sustained.

⁵ Campbell H, Amirthalingam G et al. Accelerating control of pertussis in England and Wales. *Emerg Infect Dis.* 2012 Jan;18(1):38-47.

⁶ World Health Organization (2010) Pertussis vaccines: WHO position paper. *Weekly Epidemiological Record* No 40 85: 385-400.

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