

The hexavalent DTaP/IPV/Hib/HepB (6 in 1) combination vaccine

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

Background

From autumn 2017, all babies born on or after 1 August 2017 will become 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 (ie 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 PHA immunisation webpage <http://pha.site/immunisationvaccine-preventable-diseases>

What is Infanrix hexa®?

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/antigens.¹

When will Infanrix hexa® be introduced into the infant schedule?

All babies born on or after 1 August 2017 will become eligible for the vaccine eight weeks after their birth. Infanrix hexa® vaccine is expected to be made available to order from September 2017 for use in the routine childhood primary immunisation schedule at 8, 12 and 16 weeks of age.

Infants born before 1 August 2017 should complete their primary immunisation course with pentavalent vaccine (Pediacel® or Infanrix-IPV+Hib®). Infanrix hexa® should only be given to babies born before 1 August if there is no locally held vaccine stock and no further Pediacel® or Infanrix-IPV+Hib® can be ordered. Infanrix hexa®

should also be given if pentavalent vaccine is not readily available - vaccination should never be delayed in order to obtain the pentavalent vaccine.

Why is Infanrix hexa® 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 1997. 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.

Where else is Infanrix hexa® used?

Infanrix hexa® is not a new vaccine. It is licensed for use in 97 other countries across the world including Republic of Ireland, 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.

What is 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. 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.

Is the Infanrix hexa® vaccine safe and effective?

Yes. 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 vaccines. These may include redness, swelling and tenderness at the injection site, fever, irritability, loss of appetite, diarrhoea and vomiting.

Results from clinical trials show that nearly all infants given the three dose primary vaccination course of Infanrix hexa® at 8, 12 and 16 weeks of age develop protective levels of antibodies against diphtheria (100%), tetanus (100%), pertussis (100%), hepatitis B (99.5%), polio (98-100%) and Hib (96%).²

Vaccine scheduling

What is 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 eg travel to an endemic country. The schedule should then be completed with a minimum of four weeks between subsequent doses of Infanrix hexa®.

Can Infanrix hexa® be administered at the same time as the other infant vaccines?

Yes. 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 (PCV) and MenB.

Can Infanrix hexa® be given to premature infants?

Yes. 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 (ie 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 should happen if the vaccine course is interrupted or an infant misses a scheduled dose?

If the primary course 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 should children with incomplete, uncertain or non-UK primary immunisations be given?

If the child was born before 1 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 1 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 1 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 1 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 eg if the child will be regularly returning to a country with high prevalence of hepatitis B infection.

Booster and catch-up doses

Is there a catch up programme for babies born before 1 August 2017?

No. 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 1 August 2017, will, as always, be eligible for hepatitis B vaccine if they are identified as being at increased risk of HBV.

Do infants given the hexavalent hepatitis B-containing vaccine need a booster dose of hepatitis B vaccine?

No. For infants who have completed a primary course of vaccination, a routine booster dose of vaccine is not required.

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

What are the contraindications to receiving Infanrix hexa® vaccine?

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 the Public Health Agency Duty Room on 0300 555 0119.

What are the precautions to receiving Infanrix hexa® vaccine?

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 question on premature infants above).

Vaccine storage and administration

How should Infanrix hexa® vaccine be stored?

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 Trust Pharmacy and PHA Duty Room 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 Trust Pharmacy department.

How is Infanrix hexa® vaccine presented?

- 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.

What are the steps involved in preparing 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.

How should Infanrix hexa® be administered?

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.

Is there any change in post-immunisation care recommendations?

No. The recommendations following administration of Infanrix hexa® vaccine are the same as with the administration of Pediacel® and Infanrix®-IPV+Hib vaccines.

When PCV13 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 PCV13.

For further information about administration of paracetamol, please see leaflet "Immunisations for babies up to a year old" on the PHA website: <http://www.publichealth.hscni.net/publications/immunisation-babies-year-old-english-and-10-translations>

What should happen to remaining stocks of the pentavalent DTaP/IPV/Hib vaccine?

The Infanrix hexa® vaccine is expected to be made available to order 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 or no pentavalent vaccine is readily available.

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 should happen 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, for example 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.

What actions should be taken if the immuniser forgets to reconstitute the Hib component of the vaccine and only administers the DTaP/IPV/HepB component of Infanrix hexa® in the pre-filled syringe?

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 as per employer policy. It is important to establish if the

error was a one-off occurrence or a systematic error that might require a look back exercise. In the latter case, please inform the PHA Health Protection duty room.

What 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 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

What else does Infanrix hexa® contain besides the DTaP/IPV/Hib/HepB antigens?

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).

Does Infanrix hexa® contain any preservatives such as thiomersal?

No, Infanrix hexa® does not contain thiomersal.

Does Infanrix hexa® contain any porcine gelatine?

No, Infanrix hexa® does not contain porcine gelatine.

Addressing parental concerns

What could I 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 Ireland, 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 experienced.

What do I say to a parent who is concerned about receiving a vaccine with six components in it?

It is acknowledged that some parents may be concerned that their child is receiving a six component combination vaccine. While 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 vaccines.³

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 if a parent does not want to receive a vaccine with hepatitis B in it?

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.

Other questions

Wasn’t there a concern that protection against whooping cough is lower with three component acellular pertussis (3aP) vaccines than with 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 age.³ In 2008, JCVI advised that 3aP combination vaccines could be used for primary immunisation. In 2010, the WHO also reviewed all the global data on pertussis control in countries using acellular vaccines.⁴ 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.

Are adequate Hib antibody levels made to the Infanrix hexa® DTaP/IPV/Hib/HepB combination 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.

Useful links

European Medicines Agency. Summary of the European public assessment report for Infanrix hexa®. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000296/human_med_000833.jsp&mid=WC0b01ac058001d124

Infanrix hexa® Summary of Product Characteristics. Available at: <https://www.medicines.org.uk/emc/medicine/33313>

Public Health England. Immunisation against infectious disease (The Green Book) Diphtheria, Tetanus, Pertussis, Polio, Hib and Hepatitis B chapters. Available at: <https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book>

References

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3. Centre for Disease Control (CDC). Multiple Vaccinations and the Immune System. [internet] accessed 27 March 2017. <http://www.cdc.gov/vaccinesafety/Vaccines/multiplevaccines.html>
4. World Health Organization (2010) Pertussis vaccines: WHO position paper. *Weekly Epidemiological Record* No 40 85: 385-400.



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