The hexavalent DTaP/IPV/Hib/HepB combination vaccine

Information for registered healthcare practitioners about the introduction of the hexavalent vaccine into the routine infant immunisation programme

July 2017
Key Messages

• Babies born on or after 1st August 2017 will be offered a hexavalent DTaP/IPV/Hib/HepB vaccine (Infanrix hexa®) which will protect against hepatitis B
• Hepatitis B is a viral infection that attacks the liver and can cause hepatic necrosis, cirrhosis and an increased risk of developing liver cancer
• Infanrix hexa® is licensed for use in 97 countries and approximately 150 million doses have been given to infants worldwide
• Multiple studies have shown Infanrix hexa® to be safe and highly immunogenic
• Any adverse events experienced are mild to moderate and the same as those following administration of the pentavalent vaccines (Pediacel® and Infanrix®-IPV+Hib)
• The routine infant immunisation schedule remains unchanged at 8, 12 and 16 weeks
Aims of resource

To provide information to registered healthcare practitioners about the introduction of a hexavalent DTaP/IPV/Hib/HepB vaccine in order that:

• immunisers are knowledgeable and confident in administering and discussing this vaccine with parents/carers

• high uptake of the routine infant immunisation schedule is sustained as the hexavalent vaccine replaces the pentavalent vaccine
Learning Outcomes

After completing the resource practitioners will be able to:

• Understand the rationale and evidence base for the introduction of the hexavalent DTaP/IPV/Hib/HepB combination vaccine into the routine infant immunisation programme
• Discuss the benefits of the DTaP/IPV/Hib/HepB vaccine with parents/carers
• Safely administer the vaccine
• Identify sources of additional information
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• Inclusion of hepatitis B vaccine in the routine infant immunisation programme
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Section 1 - Background

The introduction of the hexavalent DTaP/IPV/Hib/HepB combination vaccine into the routine infant immunisation programme
Introduction of a hexavalent infant vaccine

- From autumn 2017, all babies born on or after 1 August 2017 will receive a hexavalent (6 in 1) vaccine called Infanrix hexa® for their primary immunisations at 8, 12 and 16 weeks
- This hexavalent vaccine includes hepatitis B (HepB)
- It also protects against diphtheria, tetanus, pertussis, poliomyelitis and disease caused by *Haemophilus influenzae* type b (Hib)
- Infanrix hexa® will replace the pentavalent (5 in 1) infant vaccines Infanrix®-IPV+Hib and Pediacel®

Image courtesy of Glaxosmithkline

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Why is a hepatitis B containing vaccine being offered to all infants?

- In 1992, the World Health Assembly recommended every country should have a universal hepatitis B immunisation programme.
- However, as the UK is a low prevalence and low incidence country for hepatitis B, 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, 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.
- They subsequently recommended the use of the hexavalent DTaP/IPV/Hib/HepB combination vaccine for all infants.
What is hepatitis B?

- Hepatitis B is a viral infection that attacks the liver and can cause both acute and chronic disease.
- Many new infections with hepatitis B virus (HBV) are sub-clinical or may only cause a flu-like illness.
- Mostly asymptomatic in infants.
- Acute HBV infection occasionally leads to sudden and severe liver damage which can be fatal.
- Chronic HBV infection can result in progressive liver disease.
- This can lead to cirrhosis (development of scar tissue) and an increased risk of developing liver cancer.
How is hepatitis B virus (HBV) transmitted?

- Humans are the only reservoir of hepatitis B
- HBV is highly transmissible through the exchange of infected blood and bodily fluids
- It can survive outside the body for at least 7 days
- Transmission mostly occurs:
  - through vaginal or anal intercourse
  - as a result of blood-to-blood contact through percutaneous exposure (e.g. sharing of needles and other equipment by people who inject drugs or through ‘needlestick’ injuries)
  - through perinatal transmission from mother to child
- Transmission has also followed bites from infected persons although this is rare
- Transfusion-associated infection now also rare in UK as blood donors and donations are screened

Image courtesy of PHE Colindale
Clinical presentation

- Many new infections are subclinical showing no signs of infection
- If symptomatic, symptoms of acute infection start insidiously and may present as flu like illness with or without mild fever or symptoms may be non-specific
- Anorexia, nausea, vomiting and aching in the right upper abdomen may be present
- Followed by malaise, decreased appetite, joint pain and jaundice with progressive darkening of urine and lightening of the faeces
- Symptoms may last several weeks to months
- In those with symptoms not suggestive of hepatitis, infection only detected through abnormal liver function tests and/or presence of serological markers of infection e.g. hepatitis B surface antigen (HBsAg)
Stages of hepatitis B infection

Incubation period
• Average incubation period is 60-90 days but can vary between 40-160 days

Infectious period
• Those with detectable surface antigen (HBsAg) in serum are considered to be infectious
• Those who also have the e-antigen marker (HBeAg) are the most infectious

Acute stage
• Within the first 6 months of infection
• Those who clear the virus during this stage will be immune for life

Chronic stage
• Defined as persistence of HBsAg in the serum for six months or longer
• Referred to as carriers and remain infectious
• Children less than 6 years of age who become infected with hepatitis B virus are the most likely to develop chronic infection
Treatment and prevention

• No specific treatment is available for acute hepatitis B
• Supportive treatment may be indicated for severe clinical manifestations e.g. replacement of fluids lost from vomiting and diarrhoea
• Chronic hepatitis B infection can be treated with oral antivirals which can slow the progression of cirrhosis, reduce incidence of liver cancer and improve long term survival
• Hepatitis B vaccination is the most effective prevention
• A completed course of vaccine induces protective antibody levels in more than 95% of infants, children and young adults
• Protection lasts at least 20 to 30 years
• The vaccine has an excellent record of safety and effectiveness
• In 2015, 185 of 194 WHO Member countries (95%) had included hepatitis in their national infant immunisation programmes
Section 2 - Epidemiology of hepatitis B
UK hepatitis B epidemiology

UK is a very low-prevalence country for HepB:

- 0.3 - 0.4% UK population infected
- Prevalence of HepB infection varies across the country e.g. prevalence rates in antenatal women vary from 0.05 to 0.08% in some rural areas but rise to 1% or more in certain inner city areas
- Higher prevalence in those born in high-endemicity countries, many of whom will have acquired infection at birth or in early childhood
- Incidence of acute infection is low but is higher among those with certain behavioural or occupational risk factors
Globally, hepatitis B is one of the most common infectious diseases WHO estimates around 250 million people worldwide are chronically infected. 
Source: CDC Health Information for International Travel 2016
Section 3 -
The Infanrix hexa® vaccine
The recommended vaccine

• Brand name: Infanrix hexa®
• Multi-component inactivated vaccine marketed by GlaxoSmithKline
• Licensed for use from six weeks of age
• Routinely recommended for infants as part of the primary immunisation schedule at 8, 12 and 16 weeks
• 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

Image courtesy of GlaxoSmithKline
Who is eligible to receive Infanrix hexa® vaccine?

- 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 for NHS boards to order from 1st September 2017
- NHS board vaccine holding centres will distribute Infanrix hexa® for use in the routine childhood primary immunisation schedule
- 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 NHS board vaccine holding centres or if pentavalent vaccine is not readily available.
Is Infanrix hexa® a new vaccine?

- Infanrix hexa® is not a new vaccine
- First licensed for use in Europe in October 2000
- Licensed for use in 97 other countries including Canada, Australia and New Zealand
- Approximately 150 million doses have been given to infants in Europe and across the world
- Infanrix hexa® protects against the same five diseases (tetanus, diphtheria, whooping cough, polio and Hib) as the pentavalent vaccines Infanrix®-IPV+Hib and Pediaceł®
- The main difference is that Infanrix hexa® also offers protection against hepatitis B
Is Infanrix hexa® vaccine safe and effective?

- The safety profile of Infanrix hexa® is excellent
- Any adverse events experienced are mild to moderate
  - Same as those experienced following administration of the Pediacel® and Infanrix®-IPV+Hib vaccines
  - Include redness, swelling and tenderness at the injection site, fever, irritability, loss of appetite, diarrhoea and vomiting
- Multiple studies have shown Infanrix hexa® to be safe and highly immunogenic for all its component toxoids/antigens

Dhillon 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
Vaccine scheduling

- The infant immunisation schedule remains unchanged at eight, twelve and sixteen weeks of age
- First dose of Infanrix hexa® can be given from six weeks (if required in exceptional circumstances e.g. travel to an endemic country) but not before
- The minimum interval between doses of Infanrix hexa® is four weeks
- Infanrix hexa® can be administered at the same time as, or at any time before or after, other vaccines but a four week gap is required between a previous dose of Infanrix hexa®, Pediacel®, or Infanrix®-IPV+Hib
- If primary course is interrupted, resume but don’t repeat, allowing an interval of four weeks between the remaining doses
- As with the pentavalent vaccines, Infanrix hexa® should be given to premature infants at the appropriate (uncorrected) chronological age, according to the schedule
- Booster doses of hepatitis B will not usually be required for children vaccinated according to the routine childhood schedule
Contraindications

• 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 member of the local Health Protection team
Precautions (1)

- As for pentavalent vaccine, there are very few occasions when deferral of immunisation with Infanrix hexa® is required
- If infant has a minor illness without fever or systemic upset, immunisations can still be given
- If infant is acutely unwell, 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 evidence of current neurological deterioration, deferral of DTaP/IPV/Hib/HepB vaccination may be considered to avoid incorrect attribution of any change in the underlying condition
- Risk of deferral should be balanced against risk of infection and vaccination should be given promptly once diagnosis and/or expected course of the condition becomes clear
Precautions (2)

Premature infants

- 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

Systemic and local reactions following a previous immunisation

- 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
Infanrix hexa® vaccine composition

After reconstitution, 1 dose (0.5 ml) contains:

- Diphtheria toxoid
- Tetanus toxoid
- *Bordetella pertussis* antigens
  - Pertussis toxoid (PT)
  - Filamentous Haemagglutinin (FHA)
  - Pertactin (PRN)
- Hepatitis B surface antigen (HBs)
- Poliovirus (inactivated) (IPV)
  - type 1 (Mahoney strain)
  - type 2 (MEF-1 strain)
  - type 3 (Saukett strain)
- *Haemophilus influenzae* type b polysaccharide (polyribosylribitol phosphate, PRP)
  - conjugated to tetanus toxoid as carrier protein

Adjuvants:
- Aluminium hydroxide, hydrated (Al(OH)3)
- Aluminium phosphate (AlPO4)

Excipients:
- Lactose anhydrous
- Sodium chloride (NaCl)
- Medium 199 containing principally amino acids, mineral salts, vitamins
- Water for injections

The vaccine may contain traces of formaldehyde, neomycin and polymyxin which are used during the manufacturing process.

Infanrix hexa® does not contain any porcine gelatine or thiomersal
How is Infanrix hexa® vaccine presented?

• 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
• The lyophilised (freeze dried) Hib vaccine is presented as a white powder in a glass vial
• The vaccine is supplied in single dose packs containing the syringe, vial and two needles:
  - Green needle for reconstitution
  - Blue needle for vaccine administration

Image courtesy of Glaxosmithkline

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What are the steps involved in preparing Infanrix hexa®?

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

*DO NOT FORGET TO RECONSITUTE THE HIB COMPONENT*
Storage and administration

- Infanrix hexa® should be stored between +2°C to +8°C
- It must be stored in its original packaging to:
  - protect it from light
  - ensure the component parts are kept together
  - retain the batch number and expiry date for the entire product which is printed on the outer vaccine carton

- Infanrix hexa® should be administered intramuscularly
- Infants with a bleeding disorder should receive the vaccine by deep subcutaneous injection to reduce the risk of bleeding
- Preferred site of injection for infants under one year of age is the anterolateral aspect of the thigh
- It can be given in the same thigh as the PCV vaccine at the 8 and 16 week immunisation appointments (minimum of 2.5cm apart)
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
- In the current UK schedule, infants receive these vaccines alongside MenB and PCV vaccination at 8 and 16 weeks
- A routine recommendation to offer prophylactic paracetamol with the infant doses of MenB was introduced to reduce the rate of fever when MenB is administered with other routine vaccinations. This should continue
- Please see ‘Is your baby due their MenB vaccine?’ and ‘What to expect after immunisation: babies and young children’ available on the Health Scotland Immunisation Publications page http://www.immunisationscotland.org.uk/publications/index.aspx
- Vaccinators should remind parents/carers bringing infants to these visits to have arrangements for prophylactic paracetamol in place

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Administration of Infanrix hexa®

- Infanrix hexa® should only be supplied and administered:
  - Against a prescription written manually or electronically by a registered medical practitioner or other authorised prescriber
  - Against a Patient Specific Direction
  - Against a Patient Group Direction
  - A patient group direction (PGD) template for Infanrix hexa® will be available on the Health Protection Scotland website [http://www.hps.scot.nhs.uk/immvax/pgd.aspx](http://www.hps.scot.nhs.uk/immvax/pgd.aspx)
  - Adoption and governance of the use of this PGD is the responsibility of the NHS boards
Possible adverse reactions

- **Most commonly** reported (seen in more than 1 in 10 doses of the vaccine)
- Loss of appetite, fever (>38ºC), abnormal crying, irritability and restlessness
- Local swelling, pain and redness at the injection site
- Hypersensitivity reactions, such as angioedema, urticaria and anaphylaxis can occur but are rare, as can convulsions (with or without fever) and hypotonic-hyporesponsive episodes (also rare)
- Suspected adverse reactions should
- be reported to the MHRA using
- the Yellow Card reporting scheme at: [https://yellowcard.mhra.gov.uk/](https://yellowcard.mhra.gov.uk/)
Section 4 - The programme

Inclusion of hepatitis B vaccine in the routine infant immunisation programme

Neonatal selective immunisation programme for babies at risk of hepatitis B
Inclusion in routine immunisation programme
Who is eligible to receive Infanrix hexa® vaccine?

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Neonatal selective programme
Implications for babies at high risk of hepatitis B infection

- Babies born to mothers chronically infected with HBV or who have had acute hepatitis B during pregnancy are at risk of becoming infected with HBV
- Objective of the selective neonatal hepatitis B immunisation programme is to provide post exposure immunisation to infants born to HBV infected mothers to prevent mother to child transmission at or around the time of birth
- With the introduction of hepatitis B vaccine into the routine schedule:
  - the maternal hepatitis B screening programme will continue as it remains essential to identify unborn babies at risk of infection
  - the neonatal selective immunisation programme will continue so that high risk infants receive a dose of HepB vaccine at birth followed by a dose at four weeks of age
Why is the selective neonatal immunisation programme continuing if all infants will receive hepatitis B vaccine?

• HBV infection can be transmitted from infected mothers to their babies at or around the time of birth as infected blood from the mother passes through placenta to baby during delivery
• Babies acquiring infection at this time have a high risk of becoming chronically infected with the virus
• Over 90% of chronic infection in infants born to infected mothers after perinatal transmission can be prevented by appropriate post-exposure prophylactic vaccination starting at birth
• Timely vaccination at birth and at four weeks of age is critical to preventing infant infection
• The dose that is given to all babies at eight weeks of age (as part of the routine programme) would be too late to prevent infection in those high risk babies who are exposed at or around birth
## Hepatitis B vaccine schedule for routine and at risk infant immunisation programmes

<table>
<thead>
<tr>
<th>Age</th>
<th>Routine childhood</th>
<th>Babies born to hepatitis B infected mothers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>X*</td>
<td>✔</td>
</tr>
<tr>
<td>4 weeks</td>
<td>X</td>
<td>✔</td>
</tr>
<tr>
<td>8 weeks</td>
<td>✔ DTaP/IPV/Hib/HepB (Infanrix hexa)</td>
<td>✔</td>
</tr>
<tr>
<td>12 weeks</td>
<td>✔ DTaP/IPV/Hib/HepB (Infanrix hexa)</td>
<td>✔</td>
</tr>
<tr>
<td>16 weeks</td>
<td>✔ DTaP/IPV/Hib/HepB (Infanrix hexa)</td>
<td>✔</td>
</tr>
<tr>
<td>1 year</td>
<td>X</td>
<td>✔</td>
</tr>
</tbody>
</table>

*Babies born to hepB negative mothers but going home to a household with another hepatitis B infected person may be at immediate risk of hepatitis B infection so should be given a monovalent dose of hepatitis B vaccine before discharge from hospital. All other babies, for example those in a PWID environment, without a known hepatitis B infected person, should be vaccinated according to the routine childhood schedule.

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Blood tests for high risk infants

• Although hepatitis B vaccine is highly effective at preventing infection if given at birth, a very small number of infants may still acquire infection despite vaccination and immunoglobulin
• Testing high risk infants at 12 months of age prior to vaccination is important to enable timely assessment of their infection status
• Finding out if infant is infected at this point can reduce risk of long term complications and disease in later life
• The purpose of the 12 month blood test is to check for infection, not to check or measure response to the vaccine
• Numerous studies have already demonstrated that infants make a protective response to a course of hepatitis B given in the first year of life
## Booster doses for high risk infants

**12 month hepatitis B booster:**
- A further dose of monovalent HepB vaccine should be given at one year of age, alongside a test for HBsAg
- Testing at one year of age important to identify babies who have become chronically infected with hepatitis B despite vaccination

**Pre-school hepatitis B booster:**
- Increasing evidence that protection is long-lasting and benefits of booster doses therefore limited
- A further dose of hepatitis B-containing vaccine at 3 years and 4 months is no longer recommended for those children who have completed their routine primary immunisations with hexavalent DTaP/IPV/Hib/HepB vaccine
- Pre-school booster vaccine appointment provides an opportunity to check child has been appropriately managed, i.e. fully immunised against hepatitis B and tested for infection
Section 5 - Sources of information
Healthcare practitioner questions

Further information and commonly asked questions about the inclusion of hepatitis B containing vaccine in the routine and selective infant immunisation schedule are available in the following documents:

• 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

• The hexavalent DTaP/IPV/Hib/HepB combination vaccine Information for healthcare practitioners about the neonatal selective immunisation programme for babies at high risk (babies born to hepatitis B positive mothers) of hepatitis B

Further sources of information

- Health Protection Scotland (PGD) http://www.hps.scot.nhs.uk/immvax/pgd.aspx
- Health Scotland – Immunisation Scotland webpages (Parent/carer information) http://www.immunisationscotland.org.uk
- Infanrix hexa® Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/medicine/33313
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