immunogenicity of Shiga toxin produced by the organism. While vaccination against EPEC has to be directed towards susceptible human populations, there are two possible approaches with regard to EHEC, namely vaccination of either humans or the animal reservoir, cattle. Studies of vaccine candidates are ongoing *in vitro*, in *animal* models, and in healthy subjects. For both pathogens, however, the development of vaccines would not in itself serve to eradicate the spread of infections and would need to be accompanied by public health campaigns to increase food hygiene and monitoring of water supplies and facilities.[1]

Enterotoxigenic *E. coli* (ETEC) is a major cause of travellers' diarrhoea. A phase II placebo-controlled study[2] found that a vaccine containing heat-labile enterotoxin from ETEC given as a skin patch (2 patches applied 2 to 3 weeks apart), reduced the risk of moderate to severe travellers' diarrhoea by 75% and severe diarrhoea by 84%. In vaccinated travellers who got diarrhoea, the illness was significantly shorter and milder.

Further references.[3-7]

1. Horne C, *et al.* Current progress in enteropathogenic and enterohemorrhagic Escherichia coli vaccines. *Expert Rev Vaccines* 2002; **1:** 483–93.
2. Frech SA, *et al.* Use of a patch containing heat-labile toxin from Escherichia coli against travellers' diarrhoea: a phase II, randomised, double-blind, placebo-controlled field trial. *Lancet* 2008; **371:** 2019–25.
3. Boedeker EC. Vaccines for enterotoxigenic Escherichia coli: current status. *Curr Opin Gastroenterol* 2005; **21:** 15–9.
4. Steffen R, *et al.* Vaccination against enterotoxigenic Escherichia coli, a cause of travelers' diarrhea. *J Travel Med* 2005; **12:** 102–7.
5. Walker RI, *et al.* Ad Hoc ETEC Technical Expert Committee. Analysis of strategies to successfully vaccinate infants in developing countries against enterotoxigenic E. coli (ETEC) disease. *Vaccine* 2007; **25:** 2545–66.
6. Goldwater PN. Treatment and prevention of enterohemorrhagic Escherichia coli infection and hemolytic uremic syndrome. *Expert Rev Anti Infect Ther* 2007; **5:** 653–63.
7. Serna A, Boedeker EC. Pathogenesis and treatment of Shiga toxin-producing Escherichia coli infections. *Curr Opin Gastroenterol* 2008; **24:** 38–47.

Gas-gangrene Antitoxins

Antitoxinas de la gangrena gaseosa.

ATC — J06AA05.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Gas-gangrene Antitoxin (Novyi); Immunoserum Gangraenicum (Clostridium Novyi)). A sterile preparation containing the specific antitoxic globulins that have the power of neutralising the alpha toxin formed by *Clostridium novyi*. It has a potency of not less than 3750 international units/mL. It should be stored at 2° to 8°, and not be allowed to freeze.

The BP 2008 states that Nov/Ser may be used on the label.

The BP 2008 gives Gas-gangrene Antitoxin (Oedematiens) as an approved synonym.

Ph. Eur. 6.2 (Gas-gangrene Antitoxin (Perfringens); Immunoserum Gangraenicum (Clostridium Perfringens)). A sterile preparation containing the specific antitoxic globulins that have the power of neutralising the alpha toxin formed by *Clostridium perfringens*. It has a potency of not less than 1500 international units/mL. It should be stored at 2° to 8°, and not be allowed to freeze.

The BP 2008 states that Perf/Ser may be used on the label.

Ph. Eur. 6.2 (Gas-gangrene Antitoxin (Septicum); Immunoserum Gangraenicum (Clostridium Septicum)). A sterile preparation containing the specific antitoxic globulins that have the power of neutralising the alpha toxin formed by *Clostridium septicum*. It has a potency of not less than 1500 international units/mL. It should be stored at 2° to 8°, and not be allowed to freeze.

The BP 2008 states that Sep/Ser may be used on the label.

Ph. Eur. 6.2 (Gas-gangrene Antitoxin, Mixed; Immunoserum Gangraenicum Mixtum). It is prepared by mixing Gas-gangrene Antitoxin (Novyi), Gas-gangrene Antitoxin (Perfringens), and Gas-gangrene Antitoxin (Septicum) in appropriate quantities. It has a potency of not less than 1000 international units/mL of Gas-gangrene Antitoxin (Novyi), not less than 1000 international units/mL of Gas-gangrene Antitoxin (Perfringens), and not less than 500 international units/mL of Gas-gangrene Antitoxin (Septicum). It should be stored at 2° to 8°, and not be allowed to freeze.

The BP 2008 states that Gas/Ser may be used on the label.

Profile

Gas-gangrene antitoxins have been used for the treatment of gas gangrene and for prophylaxis in patients at risk after injury. They are now seldom used and have been superseded by antibacterials. Monovalent gas-gangrene antitoxins have been little used in practice owing to the difficulty of rapidly identifying the infecting organism.

Preparations

Ph. Eur.: Gas-gangrene Antitoxin (Novyi); Gas-gangrene Antitoxin (Perfringens); Gas-gangrene Antitoxin (Septicum); Mixed Gas-gangrene Antitoxin.

Proprietary Preparations (details are given in Part 3)

Cz.: Gasea†.

Gonococcal Vaccines

Gonorrhoea Vaccines; Vacunas de la gonorrea.

Profile

Several experimental gonococcal vaccines, produced usually from the surface antigens of *Neisseria gonorrhoeae*, have been investigated.

Haemophilus Influenzae Vaccines

Vacunas de Haemophilus influenzae.

ATC — J07AG01 (B, purified antig. conjugate).

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Haemophilus type b Conjugate Vaccine; Vaccinum Haemophili Stirpe B Conjugatum). A liquid or freeze-dried preparation of a polysaccharide, polyribosylribitol phosphate (PRP), derived from a suitable strain of *Haemophilus influenzae* type b, covalently bound to a carrier protein. The carrier protein, when conjugated to PRP, is capable of inducing a T-cell-dependent B-cell immune response to the polysaccharide. Carrier proteins currently approved are diphtheria toxoid, tetanus toxoid, CRM 197 diphtheria protein, and meningococcal group B outer membrane protein (OMP). It should be stored at 2° to 8° and protected from light.

The BP 2008 states that Hib may be used on the label.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Erythema multiforme and transient cyanosis of the lower limbs have been reported rarely in children receiving haemophilus influenzae-containing vaccines.

Effects on the nervous system. Guillain-Barré syndrome has been reported[1] after vaccination with haemophilus influenzae conjugate vaccines in a small number of infants. In one report, onset of symptoms occurred within 1 week of vaccination of 3 infants with an haemophilus influenzae conjugate vaccine (diphtheria toxoid conjugate). However, a causal relationship has not yet been established.

1. D'Cruz OF, *et al.* Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome) after immunization with Haemophilus influenzae type b conjugate vaccine. *J Pediatr* 1989; **115:** 743–6.

Interactions

As for vaccines in general, p.2202.

Antineoplastics. Haemophilus influenzae infection occurred in a child who had received antineoplastic therapy despite having completed a primary course of immunisation before the neoplasia was diagnosed.[1] A subsequent booster dose produced an adequate antibody response. Antineoplastic therapy may have impaired the T-cell response to infection.

1. Jenkins DR, *et al.* Childhood neoplasia and Haemophilus influenzae type b vaccine failure. *Lancet* 1996; **348:** 131.

Diphtheria, tetanus, and pertussis vaccines. Some haemophilus influenzae conjugated vaccines may be mixed with diphtheria, tetanus, and pertussis vaccines before administration without adversely affecting the immunogenicity of the components[1,2] although there has also been a report of reduced immunogenicity.[3] Manufacturers may provide further information on compatibility.

1. Miller MA, *et al.* Safety and immunogenicity of PRP-T combined with DTP: excretion of capsular polysaccharide and antibody response in the immediate post-vaccination period. *Pediatrics* 1995; **95:** 522–7.
2. Mulholland EK, *et al.* The use of Haemophilus influenzae type b-tetanus toxoid conjugate vaccine mixed with diphtheria-tetanus-pertussis vaccine in Gambian infants. *Vaccine* 1996; **14:** 905–9.
3. Eskola J, *et al.* Randomised trial of the effect of co-administration with acellular pertussis DTP vaccine on immunogenicity of Haemophilus influenzae type b conjugated vaccine. *Lancet* 1996; **348:** 1688–92.

Uses and Administration

Haemophilus influenzae (Hib) vaccines are used for active immunisation against *Haemophilus influenzae* type b infections. Vaccines are prepared from the capsular polysaccharide of *H. influenzae* type b and immunogenicity, especially in young children, is improved by linking the polysaccharide to a protein carrier to form a conjugate vaccine.

Different proprietary vaccines may be conjugated to differing proteins but are generally regarded as interchangeable.

Haemophilus Influenzae Conjugate Vaccine (Diphtheria Toxoid Conjugate) (PRP-D) consists of the purified capsular polysaccharide of *Haemophilus influenzae* type b covalently linked to diphtheria toxoid.

Haemophilus Influenzae Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) (HbOC) consists of oligosaccharides derived from the purified capsular polysaccharide of *Haemophilus influenzae* type b covalently linked to a non-toxic variant of diphtheria toxin isolated from *Corynebacterium diphtheriae*.

Haemophilus Influenzae Conjugate Vaccine (Meningococcal Protein Conjugate) (PRP-OMP or PRP-OMPC) consists of the purified capsular polysaccharide of *Haemophilus influenzae* type b covalently linked to an outer membrane protein complex of *Neisseria meningitidis* group B.

Haemophilus Influenzae Conjugate Vaccine (Tetanus Toxoid Conjugate) (PRP-T) consists of the purified capsular polysaccharide of *Haemophilus influenzae* type b covalently linked to tetanus toxoid.

For primary immunisation either combined vaccines or single-component Haemophilus influenzae vaccines may be used.

In the UK, a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and Haemophilus influenzae vaccine (p.2212) is used. Children over 1 year of age and under 10 years of age who have not been immunised against *Haemophilus influenza* or have not completed a primary vaccination course of diphtheria, tetanus, pertussis, or polio, should be given 3 doses of a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and *Haemophilus influenzae* vaccine. Those who have completed a primary vaccination course of diphtheria, tetanus, pertussis, and polio, should receive a single dose of a combined *Haemophilus influenzae* and meningococcal C conjugate vaccine. Routine use in children older than 10 years or adults is not recommended in the UK, but asplenic children (over 10 years of age) and adults who have not been previously immunised should receive two doses of combined *Haemophilus influenzae* and meningococcal C conjugate vaccine, two months apart.

In the USA, primary immunisation is also carried out in conjunction with diphtheria, tetanus, and pertussis vaccination. If a meningococcal protein conjugate vaccine is used, only 2 doses are given for the primary course. A reinforcing dose using any of the available vaccines is given at 12 to 15 months of age.

Where compatibility has been shown, Hib vaccines may be mixed immediately before use with diphtheria, tetanus, and pertussis vaccines (but see Interactions, above).

Preparations

Ph. Eur.: Haemophilus Type b Conjugate Vaccine.

Proprietary Preparations (details are given in Part 3)

Arg.: PedvaxHIB†; ***Austral.:*** Hiberix; HibTITER†; PedvaxHIB; ***Austria:*** Act-HIB; HibTITER; ***Belg.:*** Act-HIB; Hiberix†; HibTITER†; ***Braz.:*** Act-HIB†; Hiberix†; PedvaxHIB; Vacina Conj Com Proteina Tetanica Contra Haemophilus influenzae Tipo B; Vacina Conj Contra Haemophilus Influenzae Tipo B; ***Canad.:*** Act-HIB; PedvaxHIB; ***Chile:*** Act-HIB; ***Cz.:*** Act-HIB; Hiberix; HibTITER†; ***Denm.:*** Act-HIB; HibTITER†; ***Fin.:*** Hiberix†; HibTITER†; ***Fr.:*** Act-HIB; ***Ger.:*** Act-HIB†; HibTITER†; PedvaxHIB†; ***Gr.:*** Act-HIB; Hiberix; HibTITER†; ***Hong Kong:*** Act-HIB; Hiberix; PedvaxHIB; ***Hung.:*** Act-HIB; ***India:*** Hiberix; Vaxim HIB; ***Indon.:*** Act-HIB; Hiberix; PedvaxHIB; ***Irl.:*** Act-HIB; Hiberix; HibTITER†; ***Israel:*** Act-HIB; HibTITER†; PedvaxHIB†; ***Ital.:*** Act-HIB; Hiberix; HibTITER†; Vaxem Hib; ***Malaysia:*** Act-HIB†; Hiberix; PedvaxHIB†; ***Mex.:*** HibTITER†; PedvaxHIB; Vaxem Hib†; ***Neth.:*** Act-HIB; Hiberix; ***Norw.:*** Act-HIB; ***NZ:*** Hiberix; HibTITER†; ***Philipp.:*** Act-HIB; Hiberix; Vaxem Hib; ***Pol.:*** Act-HIB; Hiberix; HibTITER; PedvaxHIB; ***Port.:*** Hiberix; HibTITER†; ***Rus.:*** Hiberix (Хиберикс); ***S.Afr.:*** Act-HIB; Hiberix; ***Singapore:*** Act-HIB; Hiberix; PedvaxHIB†; ***Spain:*** Act-HIB; Hiberix; HibTITER; ***Swed.:*** Act-HIB; HibTITER†; ***Switz.:*** Hiberix; ***Thai.:*** Act-HIB; Hiberix; PedvaxHIB; Vaxem Hib; ***Turk.:*** Act-HIB; Hiberix; PedvaxHIB; ***UK:*** Act-HIB†; Hiberix; ***USA:*** Act-HIB; HibTITER; OmniHIB; PedvaxHIB; ProHIBiT†; ***Venez.:*** Act-HIB†; Hiberix.

Haemophilus Influenzae and Hepatitis B Vaccines

Vacunas de Haemophilus influenzae y la hepatitis B.

ATC — J07CA08.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Haemophilus influenzae type b (Hib) conjugate and hepatitis B vaccines are available in some countries for active immunisation as part of the primary immunisation of infants born to HBsAg-negative mothers. In the USA, an Haemophilus influenzae type b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccine is used. It is given in a schedule of 3 doses, 0.5 mL being given intramuscularly at 2 months, 4 months, and 12 to 15 months of age. Use in infants less than 6 weeks old is not recommended.