New Medicine Assessment

Haemophilus type b and Meningococcal group C conjugate vaccine – Community Supply to Adults with Respiratory Conditions

Recommendation: BLACK

- NOT recommended for use by the NHS in Lancashire and South Cumbria.
- Includes medicines that NICE has not recommended for use and terminated technology appraisals, unless there is a local need.

This category includes medicines for which there is insufficient evidence of their effectiveness.

Summary of Evidence

There is no robust clinical evidence to support immunisation of adults with severe recurrent COPD exacerbations with Haemophilus type b and Meningococcal group C conjugate vaccine.

However, within the British Thoracic Society Guidelines for bronchiectasis in adults, assessment of Haemophilus Influenza Type B (Hib) is mentioned for use as a diagnostic tool for primary antibody deficiency.[1]

Details of Review

Name of medicine (generic & brand name)**:**

Menitorix - Haemophilus type b and Meningococcal group C conjugate vaccine

Strength(s) and form(s):

Powder and solvent for solution for injection

After reconstitution, each 0.5 ml dose contains:

Haemophilus type b polysaccharide (polyribosylribitol phosphate) 5 micrograms

conjugated to tetanus toxoid as carrier protein 12.5 micrograms

Neisseria meningitidis group C (strain C11) polysaccharide 5 micrograms

conjugated to tetanus toxoid as carrier protein 5 micrograms

Excipients with known effect:

This product contains sodium 75 micromoles per dose

Dose and administration:

Menitorix should be given by intramuscular injection only, preferably in the anterolateral thigh region. In children 12 to 24 months of age, the vaccine may be administered in the deltoid region.

Menitorix should under no circumstances be administered intravascularly, intradermally or subcutaneously.

Menitorix is not intended for use in adults.

BNF therapeutic class / mode of action

Bacterial Vaccines

Licensed indication(s):

Active immunization of infants from the age of 2 months and toddlers up to the age of 2 years for the prevention of invasive diseases caused by Haemophilus influenzae type b (Hib) and Neisseria meningitidis group C (MenC).

Proposed use (if different from, or in addition to, licensed indication above):

Active immunisation of adults with severe recurrent COPD exacerbations / bronchiectasis (unlicensed indication). This would be in specific cases with particular concern so this would be on a case by case basis rather than all patients.

N.B. Menitorix is not intended for use in adults.

Current standard of care/comparator therapies:

- Childhood vaccination programme

Relevant NICE guidance:

N/A

Background and context

A request came in from East Lancs CCG as their GPs were being asked by respiratory consultants to provide vaccinations (Prevenar 13 weeks apart and Menitorix) due to low antibody levels.

GPs are not commissioned to provide this service so have referred the patients back to the original consultant who made the request. The consultant has highlighted that it is more practical for the patient to attend the GP practice to receive the vaccinations.

Therefore, East Lancs CCG have asked MLCSU to review the applicable evidence in order to make a recommendation.

Vaccines against Hib were first produced in the early 1970s and they contained purified capsular polysaccharide. These vaccines were effective in children over 18 months of age, but failed to protect younger children, in whom the risk of disease was highest. The development of conjugate Hib vaccines overcame this problem. In conjugate vaccines, the capsular

polysaccharides were linked to proteins, improving the vaccine's immunogenicity, particularly in children less than one year of age. In 1992, Hib conjugate vaccine was introduced into the routine UK immunisation schedule. Hib conjugate vaccine was originally administered as a separate vaccine. In 1996, combination vaccines (DTwP/ Hib) were introduced, and in 2004, Hib vaccine combined with DTaP and IPV (DTaP/IPV/Hib) became available.

In 2003, a booster campaign was implemented with call-back of children aged six months to four years (Chief Medical Officer et al., 2004). In 2006, following studies that showed that protection against Hib waned during the second year of life, booster dose (combined with MenC as Hib/MenC) was introduced.5

There is therefore a cohort of adults, born before 1990, who will not have been immunised.

Infection is widely considered to be a major contributor to the pathogenesis and clinical course of COPD, particularly its acute exacerbations. Chronic and persistent infection by non- typeable Haemophilus influenzae (NTHi) ie non Hib, contributes to almost half of the infective exacerbations caused by bacteria.[2] NTHi has been one of the most isolated pathogens at both stable and exacerbation states of COPD.

The considerable clinical problems caused by NTHi with regard to COPD exacerbations and otitis media has prompted the scientific community to investigate whether a vaccine can be developed against the pathogen.[3] The search has been intensified due to a steady increase in antibiotic resistance and a trend of more invasive infections caused by NTHi over the last decade.

Whereas, a highly efficient glycoconjugate vaccine has previously been developed against Hib, an identical strategy cannot be employed against NTHi due to the lack of a polysaccharide capsule. Vaccine development efforts have thus been concentrated on identifying NTHi surface structures that are immunogenic, have low antigenic variability, and are conserved across this genetically highly heterogeneous species.

Two of these antigens, fused into one protein, Protein E-PilA, are together with Protein D currently being tested by GlaxoSmithKline in a phase IIb proof-of-concept clinical trial (randomized, observer-blind, placebo-controlled, and multicentric) for infection prophylaxis in COPD patients (50–70 years old). Notably, the M. catarrhalis ubiquitous surface protein A2 (UspA2) is also included in the vaccine so that an immune response against both exacerbation-causing pathogens could be elicited by the same preparation. This clinical study (NCT03281876)[4] is the only one currently being conducted on NTHi (and M. catarrhalis) according to clinicaltrials.gov, and as the investigations are on-going, the results are currently unknown.

Within the Green Book[5] exceptions to the normal childhood vaccination programme are listed. Children and adults with asplenia or splenic dysfunction may be at increased risk of invasive Hib infection. Children and adults with early complement deficiency (e.g. C1, 2, 3 or 4 deficiencies) may also be at increased risk of invasive Hib infection. Given the increased risk, additional vaccinations against Hib disease are advised for individuals who develop asplenia or splenic dysfunction or when complement deficiency is diagnosed depending on age and vaccination history. Also Individuals with immunosuppression and HIV infection (regardless of CD4 count) should be given Hib-containing vaccines in accordance with the Green Book recommendations. This is also recommended within the BHIVA Guidelines.[6]

Summary of evidence

Summary of efficacy data in proposed use:

British Thoracic Society Guidelines for bronchiectasis in adults

Evaluation of functional antibody responses should include measurements of antibody levels to T cell dependent protein or glycoprotein antigens and T cell independent polysaccharide antigens. In clinical practice analysis of T cell dependent antibody function is usually assessed by analysis of tetanus toxoid antibodies or Haemophilus Influenza Type B (Hib) polysaccharide capsule antigen coupled to a carrier protein (conjugate vaccine).

Antibody levels below protective thresholds following test immunisation are believed to indicate impaired vaccine response and a functional antibody deficiency syndrome.

A number of studies have looked at the clinical use of measurement of baseline and post vaccination Hib antibody levels in the diagnosis of immune deficiency in patients with bronchiectasis. Reduced Hib vaccine responses have been reported by a Spanish study, whilst two UK studies showed that almost all patients with absent Hib antibodies mounted protective antibody responses post- test immunisation and concluded that measurement of HIB antibodies were not essential in the initial diagnostic investigation of patients with bronchiectasis.

The biological and clinical relevance of measurement of Hib antibodies is unclear given that the majority of Haemophilus Influenzae infections in patients with bronchiectasis are caused by mucosal non-typeable unencapsulated species.

Therefore, the use of Hib antibody measurements is unlikely to be clinically useful in assessment of patients with bronchiectasis and should be restricted to patient groups at increased risk of systemic Hib infection eg major antibody syndromes.

No clinical trials could be found looking at the efficacy of Menitorix in COPD patients.

However, studies are ongoing looking at vaccines against NTHi (see below).

NCT03281876

The purpose of this study is to test if the vaccine being developed is working well in COPD patients aged 40 to 80 years old to reduce episodes of worsening symptoms ("exacerbations") and to gather further information on safety and immune response.

In the current study, COPD patients with a history of acute exacerbations will receive 2 doses of the investigational vaccine or placebo intramuscularly according to a 0, 2 month vaccination schedule, in addition to standard care.

The effect of vaccination against two pathogens known to cause exacerbations (Non-typeable Haemophilus influenza [NTHi] and Moraxella catarrhalis [Mcat]) will be evaluated at pre-defined timepoints (scheduled study visits).

In addition to the scheduled study visits, additional study visit(s) and/ or phone contact(s) will take place for each acute exacerbation of COPD occurring from first vaccination up to study conclusion.

Risk of invasive Haemophilus influenzae type b (Hib) disease in adults with secondary immunodeficiency in the post-Hib vaccine era

The study hypothesized that nonvaccinated adults with chronic conditions causing immunosuppression may lack protective antibody to Hib. They assessed serum anti-Hib IgG levels and bactericidal activity in 59 patients with chronic renal failure, 30 patients with type 2 diabetes mellitus, 28 patients with chronic obstructive pulmonary disease, and 20 patients with multiple myeloma compared to 32 healthy controls of similar age.

Considering antibody at >0.15 µg/ml as the protective correlate in unvaccinated individuals, the study detected subprotective Hib antibody levels in 29% of chronic renal failure, 20% of diabetes, 14% of COPD, and 55% of myeloma patients compared to 3% of healthy controls. The relative risk of having anti-PRP IgG antibody levels below 0.15 µg/ml was significantly higher in all the patient groups than in the healthy controls, with the exception of COPD (p=0.059).[7]

New ideas on the therapeutic effect of a combination of vaccines against pneumococcal, Haemophilus influenzae type b infection, and influenza in patients with chronic obstructive pulmonary disease

This is an abstract of a Russian study which was carried out to estimate the indicators of the therapeutic effect of combination vaccination against pneumococcal, Haemophilus influenzae type b infection, and influenza in patients with chronic obstructive pulmonary disease. Clinical, bacteriological, and immunological studies, by determining the quality of life (QL), were conducted in COPD patients during a year after combination vaccination against pneumococcal, Haemophilus influenza type b infection, and influenza. No patient numbers are provided. One year after the vaccination, there were reductions in the number of COPD exacerbations by 3.7 times, in that of antibiotic therapy cycles by 3.4 times, in the levels of inflammatory mediators of interleukins 2 and 8 and interferon-γ, and in the synthesis of IgG antibodies to Streptococcus pneumoniae, Haemophilus influenzae type b, and influenza virus strains as compared to the baseline values. The authors concluded that combination vaccination against bacterial and viral infections substantially improves the major clinical parameters of COPD, positively affecting QL indicators that generally characterize the therapeutic effect of immunization. However, the Haemophilus type b and Meningococcal group C conjugate vaccine was not studied. [8]

Summary of safety data:

System Organ Class	Frequency	Adverse reactions
Clinical trials		
Metabolism and nutrition disorders	Very common	Decreased appetite
Psychiatric disorders	Very common	Irritability
	Uncommon	Crying
	Rare	Insomnia
Nervous system disorders	Very common	Drowsiness
Gastrointestinal disorders	Uncommon	Diarrhoea, vomiting
	Rare	Abdominal pain
Skin and subcutaneous tissue disorders	Uncommon	Atopic dermatitis, rash
General disorders and administration site conditions	Very common	Fever (rectal ≥ 38°C), injection site reactions (swelling, pain, redness)
	Common	Injection site reactions (including induration and nodule)
	Uncommon	Fever (rectal > 39.5°C)
	Rare	Malaise
Post-marketing experience		
Blood and lymphatic system disorders	Not known	Lymphadenopathy
Immune system disorders	Not known	Allergic reactions (including urticaria and anaphylactoid reactions)
Nervous system disorders	Not known	Febrile seizures, hypotonia, headache, dizziness
Respiratory, thoracic and mediastinal disorders	Not known	Apnoea in very premature infants (≤28 weeks of gestation) (see section 4.4)

The following adverse reactions have not been reported in association with administration of Menitorix but have occurred very rarely during routine use of licensed meningococcal group C conjugate vaccines: Severe skin reactions, collapse or shock-like state (hypotonic-hyporesponsiveness episode), faints, seizures in patients with pre-existing seizure disorders, hypoaesthesia, paraesthesia, relapse of nephrotic syndrome, arthralgia, petechiae and/or purpura

Adverse reactions considered as being at least possibly related to vaccination have been categorised by frequency per dose as follows: Very common (≥1/10) ,Common (≥1/100, <1/10), Uncommon (≥1/1,000, <1/100), Rare (≥1/10,000, <1/1,000), Very rare (<1/10,000), Not known (cannot be estimated from the available data).

N.B This safety data was collected from clinical trials in infants and children

Strengths and limitations of the evidence:

Strengths

- Theoretical assumption that Hib vaccine may have a beneficial effect in adult patients with respiratory conditions

Limitations

- No robust clinical trials to support use in proposed indication
- Not supported in the 'Green Book'

Summary of evidence on cost effectiveness:

Haemophilus type b / Meningococcal C conjugate vaccine powder and solvent for solution for injection 0.5ml vials x 1 (Menitorix) = £37.76 (Drug Tariff July 2020).

Prescribing and risk management issues:

Unlicensed indication in adults

Commissioning considerations:

Productivity, service delivery, implementation:

Currently, GPs are not commissioned to provide this service and therefore a commissioning agreement would need to be put in place to allow GPs to administer this vaccine at the request of the secondary care respiratory clinician.

Anticipated patient numbers and net budget impact:

The number of expected patients has not been provided by the requesting CCG / Trust. However, this vaccination would be limited to those patients with recurrent exacerbations / hospitalisations and would need to be on a case by case basis.

Innovation, need, equity:

N/A/

References

[1] Hil AT et al; British Thoracic Society Guidelines for bronchiectasis in adults. Thorax 2019;74 (suppl 1):1-69 https://www.brit-thoracic.org.uk/quality-improvement/guidelines/bronchiectasis-in-adults/#:~:text=%22The%20new%20BTS%20Bronchiectasis%20Guideline,multidisciplinary%20care%20for%20this%20condition%22.

[2] Y.C. Su et al; The interplay between immune response and bacterial infection in COPD; Focus on non-typeable Haemophilus influenzae. Frontiers in immunology. November 2018, Volume 9, Article 2530. https://www.frontiersin.org/articles/10.3389/fimmu.2018.02530/full

[3] T.F.Murphy. Vaccines for Nontypeable Haemophilus influenzae: the Future Is Now. Clinical and vaccine immunology Apr 2015, 22 (5) 459-466. https://cvi.asm.org/content/22/5/459

[4] A Study to Test if the Vaccine is Working Well in Chronic Obstructive Pulmonary Disease (COPD) Patients Aged 40 to 80 Years Old to Reduce Episodes of Worsening Symptoms and to

Gather Further Information on Safety and Immune Response. ClinicalTrials.gov Identifier: NCT03281876 https://clinicaltrials.gov/ct2/show/NCT03281876

[5] Green Book Chapter 16
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/147953/Green-Book-Chapter-16.pdf

[6] BHIVA Guidelines on the use of vaccines in HIV positive adults 2015
https://www.bhiva.org/file/NriBJHDVKGwzZ/2015-Vaccination-Guidelines.pdf

[7] E.Nix et al; Risk of invasive Haemophilus influenzae type b (Hib) disease in adults with secondary immunodeficiency in the post-Hib vaccine era. Clin Vaccine Immunol . 2012 May;19(5):766-71.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3346318/pdf/zcd766.pdf

[8] Kostinov M P et al; New ideas on the therapeutic effect of a combination of vaccines against pneumococcal, Haemophilus influenzae type b infection, and influenza in patients with chronic obstructive pulmonary disease. Ter Arkh . 2015;87(3):17-22.
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