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Cholera

NOTIFIABLE

The disease

Cholera is an acute diarrhoeal illness caused by the gram-negative bacterium *Vibrio cholerae*. Following colonisation of the small bowel, *V. cholerae* produces an enterotoxin that causes secretion of fluid and electrolytes and leads to painless, watery diarrhoea. Cholera is characterised by the sudden onset of profuse, watery stools with occasional vomiting. In severe disease, dehydration, metabolic acidosis and circulatory collapse may follow rapidly. Untreated, over 50% of the most severe cases die within a few hours of onset; with prompt, correct treatment, mortality is less than 1%. Mild cases with only moderate diarrhoea also occur and asymptomatic infection is common. The incubation period is usually between two and five days but may be only a few hours.

The disease is mainly water-borne through ingestion of faecally contaminated water or shellfish and other foods. Person-to-person spread may occur through the faecal–oral route. The risk to travellers even in infected areas is very small.

Cholera serogroup O1 is classified by biotype (classical or El Tor) and is further divided into subtypes (Ogawa or Inaba). Worldwide, *V. cholerae* El Tor is currently the predominant biotype and Ogawa the predominant subtype.

History and epidemiology of the disease

The last indigenous case of cholera in England and Wales was reported in 1893. Occasional imported cases occur, but the risk of an outbreak is very small in countries with modern sanitation and water supplies, and high standards of food hygiene. In England, Wales and Northern Ireland, 126 laboratory notifications of cholera from 1990 through to 2001 were reported (Lawrence and Jones, 2004). Of these, 64% were imported from the Indian subcontinent. For the latest epidemiological data on cholera cases reported in England and Wales please see: http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/Cholera/EpidemiologicalData/ Cholera due to the classical biotype of *V. cholerae* was endemic in the Ganges Delta of West Bengal and Bangladesh during the last two

centuries and caused epidemics and global pandemics. The seventh global pandemic, which started in 1961, is due to the El Tor biotype and is now widespread in Asia and Africa; Central and South America were affected in the early and mid-1990s but have largely brought the disease under control. A new serogroup of *V. cholerae* (O139), which produces similar symptoms, emerged in the Bay of Bengal in the early 1990s, is present in South-East Asia and China, and is responsible for about 15% of reported cholera cases in these regions (World Health Organization, 2004).

In 2003, 45 countries officially reported to the World Health Organization (WHO) 111,575 cases of cholera and 1,894 deaths (WHO, 2004), an overall case–fatality ratio (CFR) of 1.7%. In certain vulnerable groups and high-risk areas, the CFR reached as high as 41%. These reports of cases and deaths are considered to grossly underestimate the actual numbers due to under-reporting and the limitations of surveillance systems. Countries in Africa (particularly the Democratic Republic of Congo, Liberia, Mozambique, Somalia and Uganda) accounted for 96% of reported cases in 2003. For the latest epidemiological information from WHO on global cholera reports please see: http://www.who.int/cholera/statistics/en/index.html .

Prevention of cholera depends primarily on improving sanitation and water supplies in endemic areas and on scrupulous personal and food and water hygiene. While new oral cholera vaccines can provide individual protection against *V. cholerae* O1, their role in endemic and outbreak conditions is not yet defined (WHO, 2004). Since 1973, when the WHO removed cholera vaccination from the International Health Regulations, there has been no requirement for cholera vaccination for travel between countries (WHO, 1983).

The only cholera vaccine licensed in the UK since May 2004 is Dukoral®, a killed *V. cholerae* whole-cell (WC) vaccine with recombinant B subunit of cholera toxin (rCTB), administered orally. Intramuscular cholera vaccines are no longer recommended for use.

The whole-cell, B subunit vaccine (WC-rCTB, which used purified cholera toxin prior to the development of recombinant cholera toxin) has been evaluated for protective efficacy in trials in Bangladesh and Peru. In the trials in Bangladesh, three doses of vaccine demonstrated 85% protective efficacy (95% confidence interval 56%–94%) at six months in children aged two to 15 years and in women over the age of 15 (Clemens *et al*., 1986; Clemens *et al*., 1990).

The protective efficacy of the vaccine when given to children aged two to five years waned rapidly so that, by 36 months after administration, the cumulative protective efficacy was 26%, compared with children and adults over the age of five years in whom it was 63%. From this data, adults require two doses of vaccine and a reinforcing dose after two years. Young children require three doses of vaccine to establish effective immunity (Clemens *et al*., 1987) with a reinforcing dose after six months.

A trial in Peru using two doses of vaccine (WC-rCTB) in young adult military recruits demonstrated 86% protective efficacy (95% confidence interval, 36%–97%) at about four months (Sánchez *et al*., 1994). This trial followed an earlier trial in Peru which did not reach as high a level of protection (Taylor *et al*., 2000). In a challenge study with North American volunteers, three doses of WC-rCTB provided 64% protection (Black *et al*., 1987).

The cholera vaccination

Oral, killed cholera vaccine (Dukoral®) is the only licensed cholera vaccine available in the UK. It contains 1mg of recombinant cholera toxin B (rCTB) in a liquid suspension of four strains of killed *V. cholerae* O1, representing subtypes Inaba and Ogawa and biotypes El Tor and classical (25×10^9 bacteria in each batch). This suspension is mixed with buffer and water as indicated below.

The vaccine is thiomersal-free. It is inactivated, does not contain live organisms and cannot cause the disease against which it protects. It does not contain the A subunit of the cholera toxin which is responsible for the pathogenicity of the toxin.

Storage

Vaccines should be stored in the original packaging at +2˚C to +8˚C and protected from light. All vaccines are sensitive to some extent to heat and cold. Heat speeds up the decline in potency of most vaccines, thus reducing their shelf life. Effectiveness cannot be guaranteed for vaccines unless they have been stored at the correct temperature. Freezing may cause increased reactogenicity and loss of potency for some vaccines. It can also cause hairline cracks in the container, leading to contamination of the contents.

Presentation

Oral cholera vaccine is supplied as approximately 3ml of a whitish suspension in a glass vial. A sachet of sodium hydrogen carbonate as white granules is also supplied and should be mixed with water as described below (see Figure 14.1).

Dosage and schedule

Adults and children over six years of age

- First dose of vaccine on day 0.
- Second dose between one and six weeks after the first dose.

Each dose of vaccine should be dissolved in 150ml of the prepared buffer solution.

For continuous protection, a booster dose should be given at the appropriate interval (see page 105).

Children two to six years of age

- First dose of vaccine on day 0.
- Second dose between one and six weeks after the first dose.
- Third dose between one and six weeks after the second dose.

Each dose of vaccine should be dissolved in 75ml of the prepared buffer solution.

Administration

Food and drink should be avoided for one hour before and one hour after vaccination. Oral administration of other medicinal products should be avoided within one hour before and after administration of the vaccine.

The buffer of sodium hydrogen carbonate is supplied as effervescent granules, which should be dissolved in approximately 150ml of cool water in a disposable plastic cup. For children aged two to six years, half of the buffer solution should then be discarded. For children over six years of age and adults, the whole 150ml of buffer solution should be used (see Figure 14.1).

The appropriate volume of the solution should then be mixed with the whitish vaccine suspension to obtain a colourless, slightly opalescent fluid. The vaccine must be drunk within two hours of reconstitution.

Cholera vaccine can be given at the same time as injected vaccines.

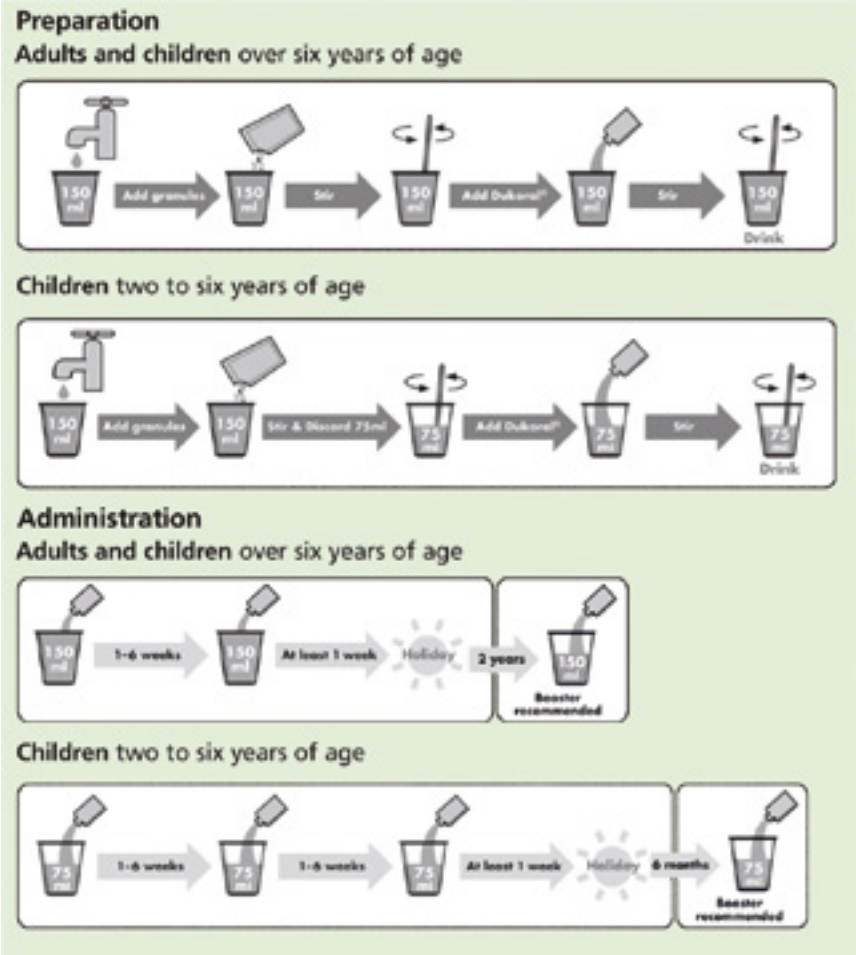

Figure 14.1 Preparation and administration of oral cholera vaccine

Disposal

Equipment used for vaccination, including used vials or ampoules, should be disposed of at the end of a session by sealing in a proper, puncture-resistant 'sharps' box (UN-approved, BS 7320). The plastic cup can be disposed of in a yellow, clinical waste bag.

Recommendations for the use of the vaccine

The objective of the cholera immunisation programme is to protect those who are most at risk of serious illness or death from the disease. Cholera vaccine

is indicated for active immunisation against disease caused by *V. cholerae* serogroup O1 in adults and child travellers from two years of age who are considered at risk for cholera. General estimates of travellers' risk of cholera based on imported cases into Europe and North America are in the order of two to three per million travellers (Mahon *et al.*, 1996; Morger *et al*., 1983; Wittlinger *et al.*, 1995; Sánchez and Taylor, 1997).

Immunisation against cholera can be considered, following a full risk assessment, for the following categories of traveller (JCVI, 2004):

- relief or disaster aid workers
- persons with remote itineraries in areas where cholera epidemics are occurring and there is limited access to medical care
- travellers to potential cholera risk areas, for whom vaccination is considered potentially beneficial.

No traveller should be required to demonstrate vaccination against cholera. Officials at a few remote borders may occasionally ask people travelling from infected areas for evidence of immunisation. Travellers who are likely to cross such borders, especially overland, should be advised to carry a signed statement on official paper that cholera vaccine is not required (Lea and Leese, 2001).

The vaccine is not recommended for prevention of the syndrome of travellers' diarrhoea since it only protects against the heat-labile toxin of enterotoxigenic *Escherichia coli* (LT-ETEC). The contribution LT-ETEC makes in travellers' diarrhoea is variable and usually small. It is only one of the many bacteria, viruses and protozoa that cause this syndrome.

Individuals at occupational risk

Vaccine is recommended for laboratory workers who may be regularly exposed to cholera in the course of their work. This would normally only include those working in reference laboratories or in laboratories attached to infectious disease units.

Primary immunisation

The primary course of the immunisation must be restarted if more than six weeks have elapsed between the first and second doses or if more than two years have elapsed since the last vaccination. These recommendations are unique to this vaccine.

Adults and children over six years of age

The standard primary course of vaccination with this vaccine against cholera consists of two doses with an interval of at least one week but less than six weeks between doses.

Children two to six years of age

The standard primary course of vaccination with this vaccine against cholera consists of three doses with an interval of at least one week but less than six weeks between doses.

If more than six weeks have elapsed between doses, the primary immunisation course should be restarted.

Immunisation should be completed at least one week prior to potential exposure to *V. cholerae* O1.

Children under two years of age

The protective efficacy of this cholera vaccine in children between one and two years of age has not been studied. Therefore, cholera vaccine is not recommended for children under two years of age.

Reinforcing immunisation

For continuous protection against cholera, a single booster dose is recommended two years after completing the primary course for adults and children over six years of age, and after six months for children aged two to six years. No clinical efficacy data have been generated on repeat booster dosing.

If more than two years have elapsed since the last vaccination, the primary course should be repeated. The need to repeat a primary course of the immunisation is unique to this vaccine.

No clinical data are available on the protective efficacy of this vaccine against cholera after administration of booster doses.

Contraindications

There are very few individuals who cannot receive oral cholera vaccine when it is recommended. Where there is doubt, appropriate advice should be sought from a travel health specialist.

The vaccine should not be given to those who have had:

- a confirmed anaphylactic reaction to a previous dose of oral cholera vaccine, or
- a confirmed anaphylactic reaction to formaldehyde or any of the components of the vaccine.

Precautions

Minor illnesses without fever or systemic upset are not valid reasons to postpone immunisation.

If an individual is acutely unwell, immunisation may be postponed until they have fully recovered. This is to avoid confusing the differential diagnosis of any acute illness by wrongly attributing any signs or symptoms to the adverse effects of the vaccine.

Cholera vaccine confers protection specific to *V. cholerae* serogroup O1. Immunisation does not protect against *V. cholerae* serogroup O139 or other species of *Vibrio*. Vaccination is not a substitute for adhering to standard protective hygiene measures to avoid cholera.

Vaccination should be delayed in individuals suffering from acute gastro-intestinal illness. Pre-existing gastro-intestinal disorders are not a contraindication to giving the vaccine.

Pregnancy and breast-feeding

No data are available on the safety of oral cholera vaccine in pregnant or breast-feeding women. There is no evidence of risk from vaccinating pregnant women or those who are breast-feeding with inactivated viral or bacterial vaccines or toxoids (Plotkin and Orenstein, 2004). If the risk of cholera is high then the vaccine should be considered in these circumstances.

Immunosuppression and HIV infection

Individuals with immunosuppression or with HIV infection (regardless of CD4 counts) should be considered for cholera vaccination in accordance with the recommendations above. However, these individuals may not develop a full antibody response if they are immunosuppressed, and vaccine protective efficacy has not been studied. Specialist advice may be required.

Further guidance is provided by the Royal College of Paediatrics and Child Health (www.rcpch.ac.uk), the British HIV Association (BHIVA) *Immunisation guidelines for HIV-infected adults* (BHIVA, 2006) and the Children's HIV Association of UK and Ireland (CHIVA) immunisation guidelines (www.bhiva.org/chiva).

Adverse reactions

Adverse events described in trials comparing individuals taking oral cholera vaccine with those ingesting buffer without the vaccine were comparable and in the range of 11% to 14% (Sánchez *et al*., 1997).

More than 1 million doses of this vaccine have been sold in Sweden and Norway. Based on passive reporting from clinical trials and post-marketing surveillance, mild gastro-intestinal symptoms (abdominal pain, cramping, diarrhoea, nausea) are the most commonly reported symptoms occurring at a frequency of 0.1% to 1%. Serious adverse events, including a flu-like syndrome, rash, arthralgia and paraesthesiae are rare, occurring in fewer than one per 10,000 doses distributed (Summary of Product Characteristics, 2004).

Management of cases, contacts and outbreaks

As cholera is a notifiable disease in the UK, for public health management of cases, contacts and outbreaks, all suspected cases should be notified to the local health protection unit immediately. Sources of infection should be identified and treated appropriately. Contacts of patients with cholera should maintain high standards of personal hygiene to avoid becoming infected. In the UK, cholera vaccine has no role in the management of contacts of cases or in controlling the spread of infection; control of the disease depends on public health measures.

Supplies

Dukoral® oral, killed cholera vaccine is supplied by Crucell (Tel: 084 4800 3907).

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