PART 4 VACCINE-PREVENTABLE DISEASES

4.1 CHOLERA

4.1.1 Bacteriology

Vibrio cholerae is a motile, curved Gram-negative bacillus. Differences in the O antigens have led to the description of more than 150 serogroups, only two of which have been found to cause cholera. Cholera is caused by enterotoxin-producing *V. cholerae* of serogroups O1 and O139 (sometimes referred to as the 'Bengal' strain). Serogroup O1 includes two biotypes (classical and El Tor), each of which includes organisms of Inaba, Ogawa and Hikojima serotypes. The ability of *V. cholerae* to persist in water is determined by the temperature, pH, salinity and availability of nutrients; it can survive under unfavourable conditions in a viable dormant state.[1] Transmission predominantly occurs when people ingest faecally contaminated food or water.

4.1.2 Clinical features

Cholera is an acute bacterial infection that is generally characterised by the sudden onset of painless, profuse, watery diarrhoea. In rare situations more than half the severe cases will die. Mild cases also occur, as does subclinical infection.[1]

The cholera toxin does not produce intestinal inflammation. The cholera toxin induces secretion of increased amounts of electrolytes into the intestinal lumen, resulting in mild to severe dehydration and, in some cases, metabolic acidosis.

4.1.3 Epidemiology

The disease is usually transmitted via food and water contaminated with human excreta. Seafood such as shellfish obtained from contaminated waters have also been responsible for outbreaks.[1] Cholera is a substantial health burden in developing countries and is considered to be endemic in Africa, Asia, South America and Central America.[2] Cholera epidemics are common in circumstances where food and water supplies can become contaminated, such as after natural disasters and civil unrest.[2] Cases of cholera in Australia (about 2 to 6 cases a year) almost always occur in individuals who have been infected in endemic areas overseas.[3] However, the overall risk of cholera to travellers with access to a safe water source and hygienic food preparation is considered to be low, even when visiting countries where cholera is endemic. The risk of infection has been estimated at 0.2 cases per 100 000 travellers from western countries, and the risk of severe disease is considerably lower,[4] although under-detection and under-reporting of cholera among travellers is likely.[2,4,5]

In 1977, a locally acquired case led to the discovery of *V. cholerae* in some rivers of the Queensland coast.[6] Because of this, health workers should be aware that sporadic cases of cholera may, on rare occasions, follow contact with estuarine waters. All cases of cholera reported since the commencement of the National Notifiable Diseases Surveillance System in 1991 have been acquired outside Australia, except for 1 case of laboratory-acquired cholera in 1996 and 3 cases in 2006.[3,7] The 3 cases in 2006, reported in Sydney, were linked and associated with consumption of raw imported whitebait.[7] These patients had no history of recent travel to known cholera-endemic areas.[7]

4.1.4 Vaccines

- ***Dukoral*** – CSL Limited and Crucell Sweden AB (inactivated whole-cell *V. cholerae* O1, in combination with a recombinant cholera toxin B subunit [rCTB]). Each 3.0 mL liquid vaccine dose vial contains heat and formalin-inactivated Inaba, Ogawa, classic and El Tor strains of *V. cholerae* O1, 31.25 x 10^9 vibrios of each, combined with 1.0 mg rCTB. The buffer consists of a sachet of effervescent granules of anhydrous sodium carbonate, sodium bicarbonate, anhydrous citric acid, sodium citrate, saccharin sodium and raspberry flavour. This formulation does not contain aspartame.

Trials of the oral cholera vaccine that contained inactivated whole-cell *V. cholerae* O1 combined with rCTB have been performed mainly in Bangladesh and Peru.[8-14] The large randomised controlled trial in Bangladesh included over 120 000 children (aged 2–15 years) and women (aged >15 years), with up to 5 years follow-up. About 13 000 children and 8 000 women received 3 doses of the study vaccine. When cholera cases in all age groups were aggregated, the protective efficacy of this vaccine (in a 3-dose regimen with inactivated *Escherichia coli* as control) was 85%, 6 months after the 3rd dose. The protective efficacy decreased to 62% after 1 year, and to 57% after 2 years.[8,10] On long-term follow-up (up to 5 years) no significant protective efficacy was observed beyond 2 years.[8,14] The efficacy of the vaccine was lower and waned more rapidly in children aged 2–5 years.[14] In this age group, while the efficacy was 100% during the first 4–6 months after vaccination, it became non-significant in the latter half of the 1st year of follow-up (during a cholera epidemic), resulting in an overall efficacy of 38% after 1 year; efficacy after 2 years was comparable. In contrast, for those aged >5 years, the efficacy estimates were 76%, 78% and 63%, respectively, at these three time

points.[8,9,14] The protective efficacy of the vaccine, over a 3-year follow-up period, was not significantly different among those who received a total of 2 doses versus those who received 3 doses (including all ages).[8,9]

A randomised controlled trial in Peru among military recruits aged 16–45 years found a vaccine efficacy of 86% against symptomatic cholera after 2 vaccine doses.[13] Another Peruvian household study showed an overall efficacy of 61% among 2–65-year olds,[12] after a booster dose given 10 months after a 2-dose primary series.[12] A field effectiveness case-control study in Mozambique, during a mass oral cholera vaccination program in an endemic population aged ≥2 years, found that 1 or more doses of the inactivated oral cholera vaccine was 78% protective (1–6 months after the 1st dose). The per-protocol effectiveness of 2 doses was 84% (0.5–4.5 months after the 2nd dose).[15]

There is structural similarity and immunologic cross-reactivity between the cholera toxin and the heat-labile toxin of *E. coli*, which is often associated with 'travellers' diarrhoea'. Therefore, it had been suggested that the rCTB-containing vaccine may also provide protection against heat-labile toxin producing enterotoxigenic *E. coli* (LT-ETEC). A study in short-term Finnish tourists[16] showed that the inactivated oral cholera vaccine also provided a 60% reduction in diarrhoea caused by LT-ETEC. A study in Bangladesh, an endemic area, showed 67% protection against LT-ETEC for 3 months only.[17] It can be expected that the inactivated vaccine will reduce the proportion of travellers' diarrhoea that is caused by LT-ETEC. Approximately 30 to 40% of travellers to developing countries contract travellers' diarrhoea, with an average of 20% of cases caused by LT-ETEC; hence, the 60% efficacy of the oral inactivated vaccine against LT-ETEC could be expected to prevent up to 15% of travellers' diarrhoea.[18-20] However, in Australia this vaccine is only registered for the prevention of cholera.

To date, there is no vaccine marketed in Australia to protect against infection with *V. cholerae* O139. An oral killed whole-cell bivalent cholera vaccine (against both serogroups O1 and O139) has been evaluated in Vietnam.[21,22] More recently, in India, an interim analysis of a cluster-randomised controlled trial reported a protective efficacy of 67% against *V. cholerae* O1 after 2 years. Specific efficacy against *V. cholerae* 0139 could not be assessed in this study, as cholera episodes caused by this serogroup were not detected.[23]

4.1.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[24] Store at +2°C to +8°C. Do not freeze. Protect from light.

Because the person to be vaccinated will be responsible for looking after the vaccine following purchase, details of how it should be transported (from pharmacy to home) and stored in the refrigerator (at home) must be carefully explained.

4.1.6 Dosage and administration

Dukoral is an oral vaccine.

Food and drink should be avoided for 1 hour before and 1 hour after administration of the inactivated cholera vaccine, as the vaccine is acid labile.

Children aged 2–6 years

Three doses are required, given a minimum of 1 week and up to 6 weeks apart. If an interval of more than 6 weeks occurs between any of the doses, re-start the vaccination course.

Dukoral is administered orally. After dissolving the buffer granules in 150 mL of water, half the solution is then poured away and the entire contents of the vaccine vial are mixed with the remaining 75 mL for administration.

Adults and children aged >6 years

Two doses are required, given a minimum of 1 week and up to 6 weeks apart. If the 2nd dose is not administered within 6 weeks, re-start the vaccination course.

Dukoral is administered orally. After dissolving the buffer granules in 150 mL of water, the contents of the vaccine vial are then added to the solution for administration.

Co-administration with other vaccines

The inactivated oral cholera vaccine can be given with, or at any time before or after, other travel vaccines, such as yellow fever or parenteral Vi polysaccharide typhoid vaccines.

However, there should be an interval of at least 8 hours between the administration of the inactivated oral cholera vaccine and oral live attenuated typhoid vaccine (see 4.1.10 *Precautions* below).

4.1.7 Recommendations

Vaccination against cholera is not an official requirement for entry into any foreign country.

Routine cholera vaccination is not recommended as the risk to travellers is very low, despite the endemicity of cholera in some countries often visited by Australians. Careful and sensible selection of food and water is of far greater importance to the traveller than cholera vaccination.

Cholera vaccination should be considered for travellers at increased risk of acquiring diarrhoeal disease, such as those with achlorhydria, and for travellers at increased risk of severe or complicated diarrhoeal disease, such as those with poorly controlled or otherwise complicated diabetes, inflammatory bowel disease, HIV/AIDS or other conditions resulting in immunocompromise, or significant cardiovascular disease.

Cholera vaccination should also be considered for travellers with considerable risk of exposure to, or acquiring, cholera, such as humanitarian disaster workers deployed to regions with endemic or epidemic cholera.

Dukoral is not registered for use in children aged <2 years and is not recommended for use in this age group.

Booster doses

Booster doses are recommended for those who are at ongoing risk of exposure to cholera.

Children aged 2–6 years who are at ongoing risk should receive a single booster dose 6 months after completion of the primary course. If the interval between primary immunisation and the booster dose is more than 6 months, primary immunisation must be repeated.

Adults and children aged >6 years who are at ongoing risk should receive a single booster dose up to 2 years after completion of the primary course. If the interval between primary immunisation and the booster dose is more than 2 years, primary immunisation must be repeated.

4.1.8 Pregnancy and breastfeeding

Cholera vaccine is not routinely recommended for pregnant or breastfeeding women.

There is limited information on the use of inactivated oral cholera vaccines during pregnancy and breastfeeding.[25]

Refer to 3.3 Groups with special vaccination requirements, Table 3.3.1 Recommendations for vaccination in pregnancy for more information.

4.1.9 Contraindications

The only absolute contraindications to cholera vaccine are:

- anaphylaxis following a previous dose of the vaccine
- anaphylaxis following any vaccine component.

4.1.10 Precautions

Postpone administration of cholera vaccine during either an acute febrile illness or acute gastrointestinal illness with persistent diarrhoea or vomiting, until recovered.

Although the vaccine is not contraindicated in people who are immunocompromised, including those with HIV infection, data on effectiveness in this population are limited.

There should be an interval of at least 8 hours between the administration of the inactivated oral cholera vaccine and oral live attenuated typhoid vaccine, as the buffer in the cholera vaccine may affect the transit of the capsules of oral typhoid vaccine through the gastrointestinal tract.

4.1.11 Adverse events

The inactivated oral cholera vaccine has a good safety profile, with similar rates of adverse events reported among vaccine and placebo clinical trial participants.[12,16,25] Mild abdominal pain, discomfort and diarrhoea were reported in post-marketing surveillance at a frequency of 0.1–1%.[26]

4.1.12 Public health management of cholera

Cholera is a notifiable and quarantinable disease in all states and territories in Australia.

Further instructions about the public health management of cholera, including management of cases of cholera and their contacts, should be obtained from state/territory public health authorities (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

4.1.13 Variations from product information

The production information for Dukoral states that a booster dose is recommended for adults 2 years after the completion of the primary vaccine course if there is an ongoing risk of cholera. The ATAGI recommends that a booster

dose is also recommended 2 years after the completion of the vaccine course for children >6 years of age if there is an ongoing risk of cholera.

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A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au.

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