14

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. Severe infection can kill within hours if left untreated. However, most people infected with *V. cholerae* remain asymptomatic, with between one and 25% developing symptoms. Of those with symptoms, the majority have a mild or moderate illness, and 10-20% experience severe disease (World Health Organization (WHO), 2017 and 2023a).

The incubation period is usually between two and five days but may be only a few hours. The severity of illness correlates with the number of *V. cholerae* bacteria ingested, previous infection, and other host and pathogen factors such as pregnancy, malnourishment, immunocompromised state, reduced ability to produce gastric acid, and having blood group O (WHO, 2017).

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 transmission is closely linked to inadequate access to clean water and sanitation facilities.

History and epidemiology of the disease

There are many serogroups of *V. cholerae* but only two, 01 and 0139 cause outbreaks.

V. cholerae O1 has caused all recent outbreaks (WHO, 2023a). Cholera serogroup O1 is classified by biotype (classical or El Tor) and is further divided into subtypes (Ogawa or Inaba).

The current (seventh) global pandemic, which started in 1961, is due to the El Tor biotype. El Tor is now the most predominant biotype worldwide and is endemic in many countries.

In 2022, a total of 472,697 cholera cases and 2,349 deaths were reported to WHO by 24 countries (WHO, 2023a). These reports are considered to grossly underestimate the actual numbers due to under-reporting and the limitations of

surveillance systems. Researchers have estimated that each year, there are 1.3 to 4 million cases and 21,000 to 143,000 deaths due to cholera (WHO, 2023a). Most affected countries report an overall cholera case fatality rate (CFR) below 1%, but in some locations, it may reach 5% in the most vulnerable settings (WHO, 2017). The burden of cholera is greatest in Africa and southern Asia. In February 2023, WHO reported that since mid-2021, there had been an upsurge of the seventh cholera pandemic, with an increase in cholera outbreaks and their geographical distribution globally (WHO, 2023b). For the latest epidemiological information from WHO on global cholera reports please see: https://www.who.int/health-topics/cholera.

Prevention of cholera depends primarily on improving sanitation and water supplies in endemic areas and on scrupulous personal and food and water hygiene. While the oral cholera vaccination can provide individual protection, it is used in risk areas as a complimentary prevention and control measure in the short to medium term while access to other prevention measures such as safe water and sanitation improve.

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 last indigenous case of cholera in England and Wales was reported in 1893. Occasional imported cases occur, but in countries with modern sanitation and water supplies, and high standards of food hygiene, the risk of an outbreak is very small. In England, Wales and Northern Ireland an average of 15 cases of cholera caused by toxigenic *Vibrio cholerae* O1 or O139 were reported each year between 2015 and 2019. In 2022, a total of 20 cases were reported (UK Health Security Agency, 2023). For the latest epidemiological data on cholera cases reported in England, Wales and Northern Ireland, please see: https://www.gov.uk/government/publications/travel-associated-infections.

The cholera vaccination

Two different oral cholera vaccines are currently available in the UK (see Table 14.1). Both are licensed for active immunisation against disease caused by *V. cholerae* serogroup 01 in adults and children from 2 years of age.

Dukoral®, is a killed, whole cell vaccine with a recombinant cholera toxin B subunit (WC-rCTB).

Vaxchora® is a live, attenuated, single dose vaccine (CVD 103-HgR).

The two vaccines have different precautions, contraindications and administration instructions, healthcare professionals must check prescribing information carefully. Intramuscular cholera vaccines are no longer recommended for use.

Inactivated WC-rCTB vaccine - Dukoral®

Dukoral®, the whole-cell, B subunit vaccine (WC-rCTB), 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 and children 6 years and older require two doses of vaccine in the primary course with a reinforcing dose within two years for those at continuing risk. Children from 2 to below 6 years of age require three doses of vaccine initially to establish effective immunity (Clemens *et al.*, 1987) with a reinforcing dose within six months for those at continuing risk (Valneva UK Ltd, 2023). See below for recommendations if more than 2 years has elapsed since the last vaccine (or more than 6 months has elapsed for children from 2 to below 6 years of age).

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).

Dukoral® 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. This suspension is mixed with buffer and water.
The vaccine is thiomersal-free. It is inactivated and cannot cause the disease against which it protects.

Live attenuated CVD 103-HgR vaccine – Vaxchora®

Vaxchora® contains live attenuated cholera bacteria (*V. cholerae* O1 classical Inaba strain CVD 103-HgR) that replicate in the gastrointestinal tract of the recipient and induce serum vibriocidal antibody and memory B cell responses (Patientric Limited, 2023).

Vaxchora® efficacy against cholera was demonstrated in a human challenge study conducted in 197 healthy adult volunteers (18 to 45 years of age) in the USA who had no prior history of exposure to cholera. A subset of Vaxchora® or placebo recipients were challenged with live *V. cholerae* at 10 days post-vaccination (n=68) or 3 months post- vaccination (n=66). A protective efficacy (in the prevention of moderate to severe diarrhoea) of 90.3% was calculated at 10 days [95% confidence interval 62.7%-100%] and 79.5% at 3 months [95% confidence interval 49.9%-100%] (Chen *et al.*, 2016).

Other studies have evaluated immunogenicity following Vaxchora® administration. The seroconversion rate following immunisation in healthy adults aged 46-64 years was non-inferior to that seen in adults aged 18-45 years (McCarty *et al.*, 2019). In a trial conducted in 550 healthy children aged 2 to <18 years, the seroconversion rate (defined as the percentages of subjects who had at least a 4-fold rise in vibriocidal antibody titer at 10 days post-vaccination compared to baseline) was 98.5% [confidence interval 96.2%-99.4%] (Patientric Limited, 2023).

Storage

Both vaccines should be stored in the original packaging at +2˚C to +8˚C and protected from light.

Dukoral® vaccine in the unopened vial and sachet, stored in the outer carton, is stable at temperatures up to 25°C for a period of 14 days. At the end of this period the product should be used or discarded (Valneva UK Ltd, 2023). This information could be helpful for travellers who have fully understood administration instructions and are able to take follow up dose(s) at home.

Vaxchora® sachets are to be removed from the refrigerator no more than 12 hours prior to reconstitution. Avoid exposure to temperatures above 25°C (Patientric Limited, 2023).

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

Dukoral® is supplied as approximately 3ml of a whitish suspension in a glass vial. A sachet of effervescent granules is also supplied and should be mixed with cool water as described in the patient information leaflet.

Vaxchora® is supplied with one active ingredient sachet with 2g of powder for oral suspension and one buffer sachet with 4.5g of effervescent powder. It is important to mix the sachets in the order described in the patient information leaflet or patient guide.

Dosage and schedule

Dukoral®

Adults and children from six years of age (two doses given orally):

- First dose of vaccine on day 0.
- Second dose at least one week later (if more than six weeks have elapsed between doses, the primary immunisation course should be re-started).

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

Children from two to below six years of age (three doses given orally):

- First dose of vaccine on day 0.
- Second dose at least one week after the first dose.
- Third dose at least one week after the second dose (if more than 6 weeks have elapsed between doses, the primary immunisation course should be re-started).

For children in this age group, each dose of vaccine should be dissolved in 75ml of the prepared buffer solution (see instructions on the patient information leaflet).

Immunisation should be completed at least 1 week prior to potential exposure to *V. cholerae* O1.

Vaxchora®

Adults and children from six years of age:

A single oral dose should be administered at least 10 days prior to potential exposure to *V. cholerae* O1.

Mix the sachets as described in the patient information leaflet with 100ml of cold or room temperature water in a cup.

Children from two to below six years of age:

A single oral dose should be administered at least 10 days prior to potential exposure to *V. cholerae* O1.

Mix the sachets as described in the patient information leaflet with 100ml of cold or room temperature water in a cup. Half (50ml) of the buffer solution should then be discarded before proceeding to add in the active component sachet 2.

Table 14.1: Cholera vaccines licensed in the UK summary

Vaccine name and manufacturer	Vaccine type	Age group	Number of doses / Schedule	Timing of booster for continuous protection	Other notes
Dukoral® Valneva UK Limited	Inactivated, oral	Adults and children from 2 yrs of age*	**Adults and children from 6 yrs of age** have 2 doses **Children from 2 to below 6 yrs of age** have 3 doses Interval of 1 week between doses**	**Adults and children from 6 yrs of age** - single booster within 2 yrs **Children from 2 to below 6 yrs of age** - single booster within 6 months	
Vaxchora® Patientric Limited	Live, oral	Adults and children from 2 yrs of age*	Single dose	No data available on booster interval	Contraindicated for immunosuppressed individuals

					Shedding of vaccine bacteria in the stools was studied for 7 days post-vaccination, and was observed in 11.3% of vaccine recipients***

* For children aged 2 to below 6 years of age, it should be noted that volumes of buffer solution administered are reduced:
- Dukoral®: the buffer is mixed with 150ml of water and half (approximately 75ml) is discarded, the remaining 75ml is mixed with the full contents of the vaccine vial.
- Vaxchora®: the buffer is mixed with 100ml of water and 50ml should be discarded before adding the active vaccine component.

** If more than 6 weeks have elapsed between doses, the primary immunisation course should be re-started.

*** Careful handwashing after visiting the toilet and preparing food for at least 14 days after taking the vaccine is recommended.

Administration

Both vaccines are given orally, and food and drink should be avoided for one hour before and one hour after vaccination.

Dukoral® SmPC also states that oral administration of other medicinal products should be avoided within one hour before and after administration of the vaccine.

There should be an interval of 2 hours between the administration of Vaxchora® and of oral typhoid vaccine Ty21a as the buffer administered with Vaxchora may affect the transit of the capsules through the gastrointestinal tract.

Follow the manufacturer's instructions carefully to ensure the vaccines are prepared correctly.

For both vaccines, for children from two to below six years of age, half of the buffer solution should be discarded, and the remaining part is mixed with the entire content of the vaccine (see above and the patient information leaflet). For children from six years of age and adults, the whole buffer solution should be used.

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

Disposal

Equipment used for vaccination, including used vials, should be disposed of at the end of a session by sealing in a proper, puncture resistant 'sharps' box according to local authority regulations and guidance in Health Technical Memorandum 07-01: Safe management of healthcare waste (Department of Health, 2013). Any unused vaccine should be disposed of in accordance with local requirements. Follow local procedures to deal with spillages of vaccines if required.

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. 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; Wittlinger *et al.*, 1995; Sánchez and Taylor, 1997; Steffan *et al.*, 2003).

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

- humanitarian aid workers.
- persons going to areas of cholera outbreaks who have limited access to safe water and medical care.
- other travellers to cholera risk areas, for whom vaccination is considered potentially beneficial (e.g. due to their occupation, activities or underlying health problems).

No traveller should be required to demonstrate vaccination against cholera.

The Dukoral® vaccine is not recommended for prevention 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, and it is only one of the many bacteria, viruses and protozoa that can cause this condition. Vaxchora® is also not recommended for the prevention of travellers' diarrhoea.

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 immunisation schedule for Dukoral® consists of two or three doses depending on age of the individual; for Vaxchora®, a single dose is used (see Table 14.1 above).

Children under two years of age

The protective efficacy of these cholera vaccines has not been studied in children below two years of age. Therefore, cholera vaccine is not recommended for this age group.

Reinforcing immunisation

Dukoral®

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

The primary course should be repeated if more than two years have elapsed since the last vaccination for adults and children from six years or if more than six months have elapsed since the last vaccination for children from two to below six years of age.

Vaxchora®

No data are available on the timing of a booster dose.

Contraindications

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

Vaccination should be postponed for those suffering from acute gastrointestinal illness or acute febrile illness.

Cholera vaccines should not be given to those who have hypersensitivity to any of the components of the vaccine, or history of allergic reaction to a previous dose of the vaccine.

Vaxchora® should not be given to those who:

- are immunosuppressed (see Chapter 6 for more detail).
- have rare hereditary problems of galactose intolerance, congenital lactase deficiency, glucose-galactose malabsorption, fructose intolerance, or sucrose-isomaltase insufficiency (Vaxchora® contains lactose and sucrose).
- have received oral or parenteral antibiotics within 14 days prior to vaccination. oral or parenteral antibiotics should be avoided for 10 days following vaccination with Vaxchora®.

The immune responses to Vaxchora® may be diminished when this vaccine is administered concomitantly with chloroquine. Administer Vaxchora® at least 10 days before beginning antimalarial prophylaxis with chloroquine. There are no data regarding concomitant use of Vaxchora® with other anti-malarial drugs.

Precautions

These vaccines confer 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 personal hygiene measures to avoid cholera.

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

Pre-existing gastro-intestinal disorders are not a contraindication to giving the Dukoral® vaccine. For Vaxchora® the degree of protection and the effects of vaccination in individuals with chronic gastrointestinal disease are unknown.

Dukoral® contains approximately 1.1 g sodium per dose. Vaxchora® contains 863 mg of sodium per dose. This should be taken into consideration by patients on a controlled sodium diet.

Vaxchora® shedding in the stools was studied for 7 days post-vaccination and was observed in 11.3% of vaccine recipients. The duration of shedding of the vaccine strain is unknown. There is a potential for transmission of the vaccine strain to non-vaccinated close (e.g., household) contacts. Vaxchora recipients should be advised to wash their hands thoroughly after visiting the toilet and before preparing food for at least 14 days after they take this vaccine. For those with immunosuppressed household or other close contacts, the inactivated vaccine, Dukoral® may be a better option.

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, Orenstein and Offit, 2013). If the risk of cholera is high, the inactivated vaccine Dukoral® should be considered in these circumstances.

Vaxchora® is a live vaccine. There are limited data from the use of Vaxchora in pregnant women. It is unknown whether Vaxchora is excreted in human milk.

Immunosuppression and HIV infection

Vaxchora® is contraindicated in individuals with immunosuppression.

Individuals with immunosuppression should be considered for inactivated cholera vaccination Dukoral® 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.

The protection afforded by cholera vaccines may be reduced in those living with HIV. 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, 2015) and the Children's HIV Association of UK and Ireland (CHIVA, 2019) travel guidelines.

Adverse reactions

Dukoral®

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).

Based on passive reporting from clinical trials and post-marketing surveillance, mild gastro-intestinal symptoms (abdominal pain, cramping, diarrhoea, and headache are the most commonly reported symptoms occurring at a frequency of 0.1% to 1%. Other adverse events, including a poor appetite, dizziness, vomiting, fever, malaise and respiratory symptoms are rare, occurring in fewer than one per 1,000 doses distributed (Valneva UK Ltd, 2023).

Vaxchora®

The most frequent reported adverse reactions are tiredness (30.2%), headache (28.3%), abdominal pain (18.4%), nausea/vomiting (17.7%), and lack of appetite (15.7%) (Patientric Limited, 2023).

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 team 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 Valneva UK Ltd (Medical Information Tel: 01506 446 608). www.valneva.co.uk.

Vaxchora® live, attenuated vaccine is supplied by Patientric Limited (Tel: 0203 515 5678). www.patientric.co.uk.

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