Cholera advice before travel

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Cholera is a low risk for travellers; however, it remains a significant public health problem. Travellers at potential risk should be offered preventive advice, including in some cases the option of vaccination.

Until the early 1990s it was common practice for intending travellers to be vaccinated against cholera. The vaccine was often administered concurrently with the typhoid vaccine, and despite the frequent incidence of significant side effects, both doctor and traveller would feel somehow satisfied that the risk of any travel-related disease was now largely avoided. Certification of cholera vaccination was often required for admission to various countries, but it is now no longer recommended by the World Health Organization (WHO) nor required by any country. The older injectable cholera and typhoid vaccines were taken off the market some years ago, and an oral inactivated cholera vaccine (Dukoral) was introduced.

The disease

Cholera is an acute diarrhoeal disease caused by toxigenic *Vibrio cholerae* bacterium. Ingestion of food or water contaminated with *V. cholerae* results in colonisation of the intestine and consequent secretion of the toxin.

The A subunit of the toxin is the enzymatically active component, which stimulates intestinal cyclic adenosine monophosphate (AMP) to transfer salts and fluid across the intestinal epithelium. This results in rapid loss of large volumes of water into the intestinal lumen. The B subunit binds the toxin to the gut and is itself nontoxic.

Although most cases are mild or asymptomatic, severe forms make cholera one of the most rapidly fatal illnesses known. Profuse watery diarrhoea, with or without vomiting, may progress to a clear form with mucus, known as 'rice water stool'. The large volume and rapid fluid loss of up to one litre per hour can result in hypotension, metabolic acidosis with hypocalcaemic tetany, renal failure and death, which may occur in hours unless adequate hydration is provided. Diseases such as cholera motivated much of the early research on appropriate rehydration therapy, and modern treatment has reduced the mortality of cholera from 50% to less than 1%.[1]

Cholera is usually transmitted from human to human, and most cases occur via contamination of food or water with faeces or vomitus. Uncooked seafood, vegetables and water are at higher risk of contamination than other foods or liquids.

The flowchart lists the serotypes of *V. cholerae*. Serogroup O1 has been the main cause of worldwide epidemics (i.e. pandemics), and is divided into the biotypes classical and El Tor, each of which is further divided into serotypes Ogawa and Inaba. The current (seventh) pandemic began in 1961 in Indonesia and reached Africa in 1970 and South America in 1991. Outbreaks in refugee situations have resulted in the deaths of over 20,000 people within one month. Serogroup O139 has been active throughout Asia since 1992.[1]

Cholera is now endemic in over 50 countries in Asia, Africa, Central and South America (Figure).[2] Significant outbreaks have occurred notably following national disasters and have been difficult to control in many countries, including Sierra Leone, South Sudan and Haiti, with the last being responsible for 47% of all reported cases in 2013.[3]

Cholera is a notifiable disease subject to quarantine and is reported in two to six people annually in Australia.[4] This equates to a risk for travellers of just one in 500,000, similar to overseas figures. However, this contrasts sharply with the incidence reported by several studies in the past. A Japanese study reported rates of cholera in Bali at 13 cases per 100,000 people, equivalent to the risk of typhoid.[5] A survey of American Embassy employees in Peru found that five out of 317 people contracted cholera, equivalent to 44 cases per 100,000 people per month of exposure.[6] An outbreak of cholera aboard a plane in 1996 affected 74 of the 336 passengers with one death.[7] A detailed review in 2007 confirmed that many cases are not reported to WHO and that worldwide the incidence

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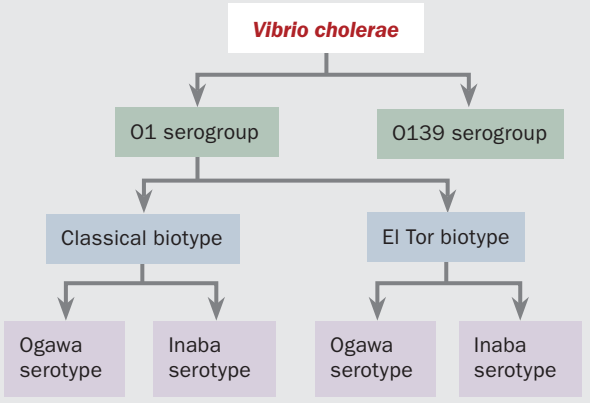
CLASSIFICATION OF TOXIGENIC *VIBRIO CHOLERAE*



Source: Travel Clinics Australia.

is not decreasing.[8] Prevention is warranted, and certainly the risk needs to be discussed with travellers, along with preventive strategies.

Diagnosis

The diagnosis of cholera is made on clinical suspicion after a patient has developed acute diarrhoeal illness. The test to request for confirmation is faecal microscopy, culture and antigen detection. The laboratory needs to be informed of the suspicion of cholera so that the specific culture for *V. cholerae* is used.

Urea and electrolyte levels should also be checked in view of the close association with water and electrolyte imbalance. Hypokalaemia may be a significant electrolyte problem and is important to detect, both because of the risk of cardiac complications and to help in the choice between intravenous and oral rehydration.

Treatment

Most cases of cholera in Australian travellers are mild and it is likely that many are missed. Rehydration is often all that is necessary; however, antibiotics may be used in more severe cases to reduce the duration and severity of illness. Antibiotic treatment may include azithromycin or ciprofloxacin.[9]

Vaccination

Although several cholera vaccines have been available in Australia, the injectable cholera vaccine was taken off the Australian market some years ago, primarily because of its lack of efficacy and poor side effect profile. In addition, a recombinant live oral *V. cholerae* CVD-HgR vaccine was withdrawn because of apparent problems with storage shelf-life and efficacy.

This leaves one vaccine available in Australia – an oral, killed recombinant B subunit/whole cell vaccine (rBS/WC), Dukoral, which is effective against both *V. cholerae* and enterotoxigenic *Escherichia coli* (ETEC), although it is not registered with the Therapeutics Goods Administration for use in Australia for ETEC-related disease. The heat and formalin killed whole cell component of this vaccine induces mucosal IgA immunity against *V. cholerae* O1 classical and El Tor biotypes, but the vaccine does not protect against the O139 serogroup. The protective efficacy of the vaccine against cholera is 85% at six months and 52% at two years.[10]

Vaccine efficacy against ETEC

There is good evidence that Dukoral is very effective against heat-labile forms of ETEC, with studies showing up to 86% efficacy at three months.[11-14] The scientific basis for this is quite strong, as the nontoxic B subunit-binding portion of the cholera toxin in the vaccine induces protective antitoxic IgA immunity. Because this *V. cholerae* subunit is antigenically similar to the B subunit of the heat-labile enterotoxin of *E. coli*, protection develops against ETEC, albeit the heat-labile form.

A 2013 Cochrane review looking at all forms of ETEC did not find sufficient evidence for the use of Dukoral.[15] However, this review did not consider the abovementioned efficacy of the vaccine against heat-labile forms of ETEC, and its finding was based on one older study of students visiting Mexico who were not vaccinated until after their arrival in Mexico. The vaccine course needs to have been completed at least one week prior to arrival.[16] Interestingly, the review did note that a demonstrably equivalent Dukoral precursor vaccine showed efficacy. Subsequently, a Spanish study of Dukoral showed 28% efficacy against all causes of travellers diarrhoea.[14] To summarise, travellers can be advised that Dukoral does provide good immunity to heat-labile forms of ETEC, equating to up to 30% of all cases of ETEC diarrhoea, and somewhat less than this for all causes of diarrhoea.[11]

Dosage and administration of vaccine

The manufacturer's recommendations for primary immunisation are to give two doses of cholera vaccine to adults and children over the age of 6 years, but three doses to children aged between 2 and 6 years, using half the amount of carbonated buffer solution for children in this younger age group. Doses need to be given one to six weeks apart, at least one hour before or one hour after food or drink, and with the last dose given at least two weeks before departure.

As mentioned above, in Australia the vaccine is approved only for the prevention of cholera; however, it may still be used 'off-label' for the prevention of ETEC in at-risk travellers. The vaccine has an excellent safety and side effect profile, and can be administered concurrently with most other vaccines, although there should be at least eight hours between its administration and administration of the oral typhoid vaccine. It can also be administered in pregnancy (category B2) and lactation.

For those at ongoing risk of exposure to cholera, a single booster

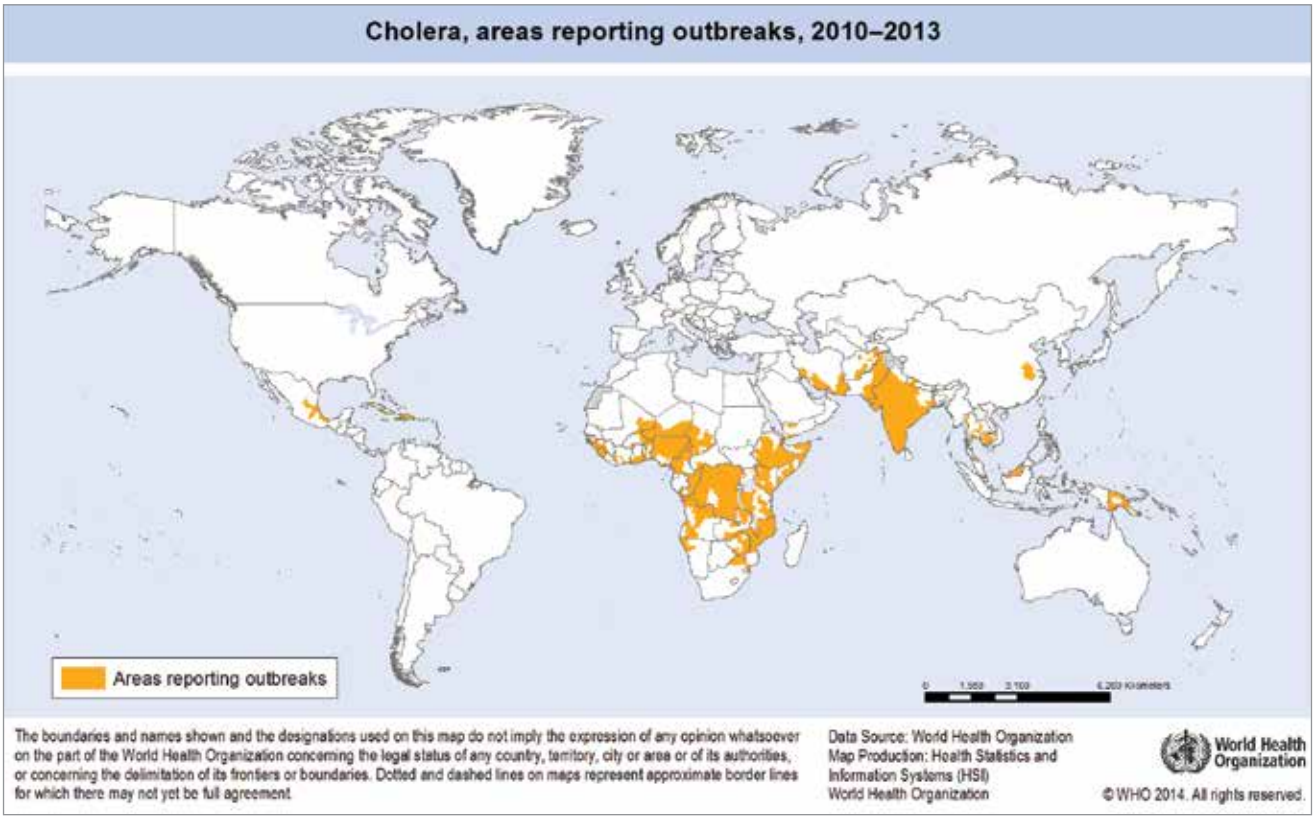


Figure. Countries reporting cholera cases 2010–2013 according to WHO, 2014.[2]

Reproduced with permission from: World Health Organization. Global Health Observatory map gallery. World: areas reporting cholera outbreaks, 2010-2013 [website]. September 2014. Available from: http://gamapserver.who.int/mapLibrary/ (accessed May 2015).[2]

dose is recommended, providing this is within two years of the previous course in adults, or six months in children aged 2-6 years. Otherwise primary immunisation with two doses given six weeks apart must be repeated.[11]

Prevention

The WHO and National Health and Medical Research Council (NHMRC) do not advocate cholera vaccination for most travellers, aside from those listed below. This is partly because of the low risk of disease, but also because careful attention to avoidance of potentially contaminated food and water is much more important, and the vaccine may give travellers a false sense of security. At our clinic, we advise travellers to follow the dictum 'boil, cook, bottle or peel' and provide verbal and written details about avoiding gastrointestinal disease in general.[17]

The vaccine is recommended by WHO in the public health setting for limiting and preventing outbreaks.[18] However, vaccination should be discussed and offered to travellers in the following high-risk categories in known endemic areas: [11]

- aid workers helping in disaster relief or refugee camps
- backpackers travelling to remote areas where access to medical care is likely to be limited
- travellers with lowered immunity or increased susceptibility – e.g. those with diabetes, inflammatory bowel disease, malabsorption or hypochlorhydria, including those taking proton pump inhibitor medication
- travellers with prolonged risk exposure – e.g. long-stay expatriates or healthcare workers.

Summary

Cholera, although not common in travellers, is a potentially serious disease. It is a low risk for most travellers; however, this risk may be underestimated. It should not be neglected in terms of offering travellers protective advice and certain groups the option of vaccination, especially emergency relief and health workers in refugee situations. MT

References

A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

COMPETING INTERESTS: Dr Cohen is Medical Director, Travel Clinics Australia.

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