



The true burden and risk of cholera: implications for prevention and control



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Cholera is a substantial health burden on the developing world and is endemic in Africa, Asia, South America, and Central America. The exact scale of the problem is uncertain because of limitations in existing surveillance systems, differences in reporting procedures, and failure to report cholera to WHO; official figures are likely to greatly underestimate the true prevalence of the disease. We have identified, through extensive literature searches, additional outbreaks of cholera to those reported to WHO, many of which originated from the Indian subcontinent and southeast Asia. Such underestimation of cholera can have important implications for decisions on provision of health interventions for indigenous populations, and on risk assessments for travellers. Furthermore, until recently, it has not been possible to implement public-health interventions in low-income countries to eliminate disease, and the prevention of cholera in travellers has been limited to restrictive guidelines. However, a vaccine against cholera is now available that has proven efficacy and tolerability in mass vaccination campaigns in low-income countries, and among travellers.

Introduction

Diarrhoeal diseases constitute a major global public-health problem, and affect indigenous populations and travellers. Up to 80% of diarrhoeal episodes in travellers (travellers' diarrhoea) are bacterial in nature, caused principally by enterotoxigenic *Escherichia coli* (30–60% of cases), but also commonly caused by *Shigella*, *Campylobacter*, and *Salmonella* spp.^{1–3} Mild-to-moderate cases of cholera, caused by the bacterium *Vibrio cholerae*, are often indistinguishable from other causes of acute diarrhoeal disease.⁴

Epidemic cholera is a strictly intestinal, non-invasive diarrhoeal disease caused by serogroups O1 and O139 of the rod-shaped, Gram-negative bacterium *V cholerae*. The O1 serogroup can be subdivided into different antigenic forms or serotypes, such as Ogawa and Inaba, and biotypes (genotypes), such as classical and El Tor.⁵ *V cholerae* produces several toxins, but the classic dehydrating diarrhoeal symptoms of cholera are caused by the cholera enterotoxin, which consists of a non-toxic B subunit and an enzymatically active A subunit, which is located in the middle of the B subunit.⁶ Cholera enterotoxin binds to the intestinal mucosal cells and causes diarrhoea and dehydration by activating the adenylate cyclase enzyme. This leads to increased production of intracellular cyclic adenosine monophosphate, which causes the mucosal cells to pump out large amounts of water and electrolytes.^{6,7}

WHO suggests that around 90% of episodes of cholera are of mild to moderate severity and are difficult to distinguish clinically from other causes of acute diarrhoea.⁴ However, cholera can be rapidly fatal in severe cases, and if left untreated, can result in up to 50% mortality.⁴ Rapid administration of fluid replacement therapy and supportive treatment can reduce mortality to around 1%.⁴

Cholera is transmitted via the faecal–oral route, with epidemics often occurring after war, civil unrest, and natural disasters when water or food supplies become contaminated with *V cholerae*, compounded by crowded

living conditions with limited sanitation. Epidemic cholera is characteristically explosive when introduced into populations lacking prior immunity. Recent evidence has provided some explanation for this, and suggests that the passage of *V cholerae* through the human gastrointestinal tract leads to a short-lived hyperinfective state. Transmission via the faeces of an infected individual is likely to cause disease with a much lower inoculum if transmission were to occur within a few hours of exposure.⁸

The magnitude of the bacterial inoculum required to give rise to severe infection with cholera is dependent on the health status of the individual. Although a high infectious dose of 10⁵–10⁸ bacteria is necessary to produce disease in healthy individuals, a much smaller inoculum can result in disease in certain populations, such as those with low levels of gastric acid.^{9–12} There is also a link between low gastric acid levels, low socioeconomic status, and cholera.⁹ Gastric acidity is a major determinant of the size of inoculum required to generate disease, because gastric acid acts as a natural barrier to *V cholerae*.^{9,12} Individuals with gastric hypochlorhydria or achlorhydria have been found to be at greater risk of developing cholera after infection with a low inoculum.¹⁰ Furthermore, an association between *Helicobacter pylori*, linked to a reduction in gastric acid, and *V cholerae* infection has been observed. This was first shown in a study in Bangladesh in 1995,¹³ and was supported by retrospective analysis of the 1991 Peruvian cholera epidemic.¹⁴

Cholera is a notifiable diarrhoeal disease in most countries. However, WHO acknowledges that only around 1% of cholera cases are actually reported.¹⁵ Cases of cholera often remain undetected for various reasons. Health advice is commonly not sought when symptoms are mild, and stools may not be routinely cultured for *V cholerae*; without microbiological isolation of the pathogen, infection is often indistinguishable from other causes of acute diarrhoea, including travellers' diarrhoea.^{4,11,16,17} Furthermore, there are limitations in

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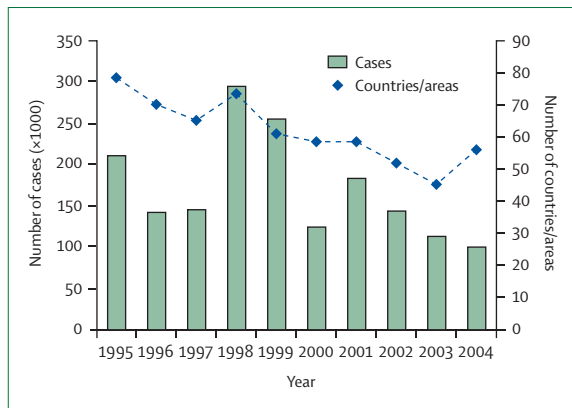


Figure 1: Number of cases of cholera reported to WHO (1995–2004)
Reproduced with permission from WHO.²¹

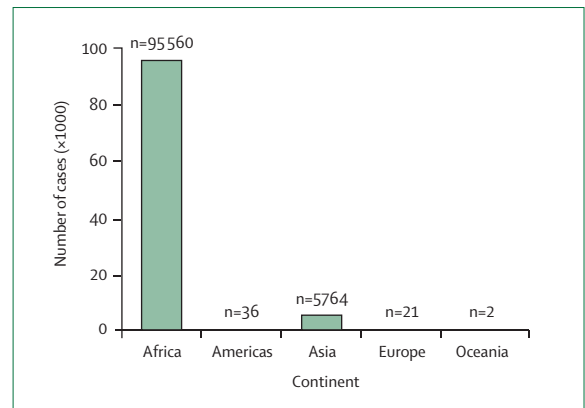


Figure 2: Number of cholera cases reported to WHO in 2004
Adapted from WHO.²¹

existing surveillance and reporting systems, as well as economic disincentives, including an impact on trade and tourism, which contribute to underestimates of the prevalence of cholera, particularly in the developing world.^{15,16}

In this Review, we present the epidemiology of cholera as determined by extensive searches within the scientific and medical literature, the wider web-based official organisation reports, and the media. We also discuss the options available for disease control, both within indigenous populations and in travellers.

Epidemiology of cholera

Endemicity and epidemics

Cholera is endemic in many parts of Africa and Asia, and has more recently become endemic in South and Central America. Outbreaks become endemic when a large proportion of the population is immune or semi-immune to infection.¹⁷ Epidemics or explosive outbreaks generally occur in underdeveloped areas with inadequate sanitation, poor hygiene, and limited access to safe water supplies, whereas in some countries, a seasonal relation for cholera epidemics has been observed.^{15,17–19}

The seventh cholera pandemic started in 1961 and is still continuing. The causative organism, *V cholerae* O1 biotype El Tor, first appeared in Indonesia and has since spread worldwide, replacing the classical strain as the leading cause of endemic cholera.^{4,20} This pandemic led to the re-emergence of cholera in Africa in 1970, and South and Central America in 1991, after the absence of cholera for more than a century.^{4,20} A new serogroup, *V cholerae* O139 Bengal, emerged in 1992 in Bangladesh. Originally restricted to areas of southeast Asia, this serogroup has now been isolated in India and Pakistan. There were concerns that the O139 serogroup could cause an eighth pandemic; however, the number of cases of cholera caused by this serogroup remain a small proportion of the total cases of cholera.^{4,6,20} Other *V cholerae* serogroups occasionally cause human illness but have not evolved into an epidemic form.⁴

Cholera cases reported to WHO

Cholera is thought to be at least as prevalent now as it was 50 years ago, with approximately 100 000–300 000 cases reported annually to WHO in 1995–2004 (figure 1). Cases reported from Africa accounted for 94% of the global total of reported cholera cases in 2004 (figure 2).²¹ The Indian subcontinent reported 81% of all notified cases from Asia, but this is not thought to indicate the true burden of disease in this part of the world.²¹

The prevalence of cholera shows no signs of decreasing; in fact, reports in 2005 clearly showed an increase in cases that year compared with previous years. WHO reported a 30% increase in cholera cases in 2005 compared with 2004,²² and China has reported that cases have increased by 298% in 2005 compared with 2004.²³ The occurrence of devastating natural disasters in late 2004 and 2005 might have led to the increased number of cholera cases reported in 2005.

Imported cholera cases reported to WHO

100 imported cases of cholera worldwide were reported to WHO during 2004,²¹ and 68 cases during 2005 (table 1).²² The rate of imported cases in Japan was higher than in western Europe and the USA. Although this could be partly attributed to increased travel to high-risk destinations, it is important to consider that surveillance is more intensive in Japan, where regular microbiological screening is done among returning travellers with diarrhoea.^{17,24}

Cholera cases not reported to WHO

The total number of cholera cases reported to WHO is likely to be a gross underestimate of the real burden of disease. Indeed, WHO estimates that, in reality, more than 120 000 people die from cholera every year, with 3–5 million cases worldwide (mortality of approximately 4%).^{15,25} Underestimation of the prevalence of cholera in any particular area can have important consequences for the indigenous population and travellers to that area. Implementation of interventions to protect the

community rely on knowledge of local disease prevalence, whereas travel health-risk assessments are based on surveillance data.

Most cholera cases reported to WHO originate in Africa: 95% in 2005,²² and 94% in 2004.²¹ Our literature searches therefore identified only a few additional reports of cholera from this continent. Conversely, many additional reports of cholera in Asia were identified that were not reported to WHO (table 2); these were often associated with natural disasters and crowded living conditions. For example, epidemics of diarrhoea were reported after flooding in Dhaka, Bangladesh, in July, 2004, during which thousands of people were admitted to hospital. Every 50th patient was screened for cholera, and 22% of laboratory specimens tested positive for *V cholerae* O1. Of more than 17 000 people affected by diarrhoeal diseases in the weeks after the floods, approximately 3740 (22%) were likely cases of cholera.²⁷ Although a review of over

600 geophysical disasters concluded that the risk of epidemics arising was negligible,⁴² there have been several reports of cholera arising from natural disasters.^{43–46}

Many countries in the Indian subcontinent and southeast Asia do not report cholera cases to WHO. For example, no cholera cases have been reported from Thailand since 1994.⁴⁷ However, a cholera epidemic occurred in southern Thailand between December, 1997, and March, 1998, with 57 strains of *V cholerae* isolated in five provinces.⁴⁸ Furthermore, *V cholerae* was isolated from stool samples in 5.4% of cases of bacterial

	Imported cases	
	2004	2005
North America		
Canada	3	7
USA	5	8
Total	8	15
Asia		
China	0	4
Hong Kong	2	0
Japan	55	33
Lebanon	0	1
Qatar	1	2
South Korea	10	0
Singapore	1	0
Total	69	40
Europe		
Austria	0	1
Belgium	1	2
Denmark	1	0
Finland	0	1
Germany	3	0
Netherlands	1	4
Norway	0	1
Poland	0	1
Russia	1	0
Sweden	1	0
UK	13	0
Total	21	10
Oceania		
Australia	2	2
New Zealand	0	1
Total	2	3
Overall total	100	68

Table 1: Annual incidence of imported cholera cases reported to WHO in 2004²¹ and 2005²²

	Country	Cases or deaths	Cause
Africa			
GIDEON ²⁶	Burkina Faso
Disaster Relief (http://www.disasterrelief.org)	Madagascar	≥1700 cases, ≥100 deaths	Cyclone
South America			
GIDEON ²⁶	Venezuela
Asia			
Qadri et al ²⁷	Bangladesh	78 laboratory-confirmed cases; >3740 estimated cases in total	Flooding
International Centre for Diarrhoeal Disease Research B ²⁸	Bangladesh	Thousands of isolations reported to the International Centre for Diarrhoeal Disease Research, Bangladesh (eg, approximately 5500 in Sept, 2004)	Continuing analysis
Dowse ²⁹	Indonesia	One case imported by an Australian tourist	..
Chung ³⁰	Indonesia	One case imported by a Korean tourist	..
Chann ³¹	Burma	"Scores of cases, several deaths"	Flooding, and damage to sewerage systems
Pacific Disaster Management Information Network ³²	Pakistan	At least 25 deaths	Afghan refugee camp
Anon ³³	Pakistan	At least 12 deaths	Contaminated water, drought
Anon ³⁴	Pakistan	Epidemic resulting in at least four deaths	..
UK Health Protection Agency ³⁵	Pakistan	One case imported by a UK tourist	..
International Society for Infectious Diseases ³⁶	Taiwan	One case imported from the Philippines	Contaminated seafood
Centers for Disease Control and Prevention ³⁷	Thailand	One case imported by a tourist from the USA	Contaminated seafood
Robert Koch-Institut ³⁸	Thailand	One case imported by a German tourist	..
Anon ³⁹	Thailand	One case imported by an Australian tourist	..
Infectious Agents Surveillance Report ⁴⁰	Thailand	Eight cases imported by Japanese tourists	..
Europe			
Strauss et al ⁴¹	Austria	Two cases imported from India	..
Oceania			
GIDEON ²⁶	New Zealand	One case, travel history unknown	..

..=not reported.

Table 2: Countries for which reports of cholera occurring during 2004 have been identified but who did not report cholera to WHO, by report

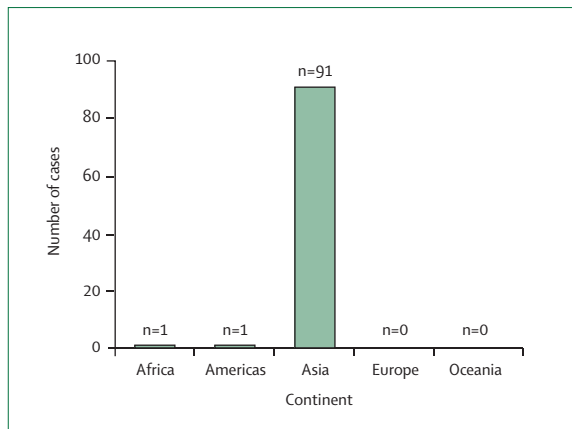


Figure 3: Source of imported cases* in 2004

*For which travel history is documented: one case imported from India to the Netherlands (van Vliet H, RIVM-CIE [Rijksinstituut voor Volksgezondheid en Milieu – Centrum voor Infectieziekten Epidemiologie], personal communication, Nov 24, 2004); one case imported from India to Germany (Seidel T, Jena University, Jena, Germany, personal communication, Oct 25, 2004).^{29,30,35–41,54,57–61}

diarrhoeal disease between January, 1995, and December, 2000, in a study of children treated in a hospital in Bangkok.⁴⁹ Similarly, a study between August, 2001, and July, 2003, found an overall incidence of 0.5 cases of cholera per 1000 individuals in North Jakarta, Indonesia, and yet there have been no reported cases since 1997.^{50,51}

Several factors contribute to the problem of under-reporting. In some countries, the current surveillance systems have serious limitations, with wide variation in the guidelines for reporting cholera cases, and some countries report only laboratory-confirmed cases.^{15,21} There are also political and economic reasons for under-reporting, including the fear of international sanctions that could lead to loss of tourism and trade. The cholera epidemic in Peru in 1991 cost the country's economy an estimated US\$770 million.¹⁵ With increasing tourism to

areas that continue to under-report cholera, such as the Indian subcontinent, there may be a reluctance to improve reporting that may otherwise reveal the true extent of the cholera burden.

Imported cholera cases not reported to WHO

In 2004, a further 25 imported cases of cholera were identified worldwide from sources other than WHO, making the total number of imported cases 125. Furthermore, these additional cases only include confirmed cases, and are therefore likely to represent a substantial underestimate of the true burden of disease. Reports of cholera identified from sources other than WHO include imported cases in New Zealand, Taiwan, and Austria (table 1 and table 2). Additional cases to those reported to WHO were identified to be imported into the UK, Australia, and Japan.^{26,29,36,39–41,52–54}

About 30 imported cases of cholera are reported to the Health Protection Agency per year in the UK (range 17–48 cases per year in 1995–2004), with approximately ten cases per year confirmed by laboratory analysis and reported to WHO.^{52,55} Most cases imported into the UK originate from the Indian subcontinent, with 32% of cases from 1990–2003 originating in India, 29% in Pakistan, and 7% in Thailand.⁵⁶

Of the 93 cases of cholera identified worldwide that were imported in 2004, and for which a travel destination could be determined, most originated from the Indian subcontinent and southeast Asia (figure 3): India (38 cases), the Philippines (36 cases), and Thailand (11 cases).^{29,30,35–41,54,57–61} Cases were also reported to originate in popular tourist destinations such as Indonesia (two cases) and Hawaii (one case), and destinations popular with travellers visiting friends and relatives, such as Pakistan (one case).^{30,35,37,54} Only two cases were reported to originate from outside Asia: one imported to the UK from Cameroon, and one to mainland USA from Hawaii (figure 3).^{37,59}

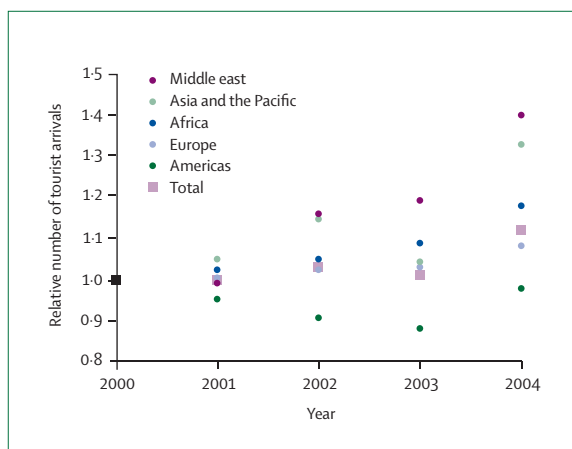


Figure 4: International tourist arrivals relative to 2000, by region
Adapted from World Tourism Organization tourism highlights.⁶³ Graph shows value relative to 2000 (black square indicates starting point as 1.0 in 2000).

Trends and issues in the importation of cholera

Worldwide, although there are relatively few imported cases of cholera reported to WHO, the incidence of such cases varies by year and by country (table 1). Although a worldwide decline from 100 to 68 imported cholera cases was reported to WHO in 2005 compared with 2004,²² the number of cases reported in England and Wales up to week 41 increased from 23 in 2005 to 44 in 2006.⁶² Furthermore, the numbers of imported cholera cases reported to WHO in 2004 were three times greater than in 2003.²¹ Many factors are likely to contribute to the increased risk of importation.

Since the 1980s, there has been a substantial increase in global travel, with a record 763 million international tourist arrivals recorded worldwide in 2004, almost 11% more than that recorded for 2003.⁶³ Greater affordability of travel, and changing trends, have led to an increase in the number of people from high-income nations

visiting tropical countries. The number of people undertaking long-haul travel is currently outgrowing intraregional travel, at 13% and 10%, respectively, and the World Tourism Organization predicts that this trend will continue in the long term.⁶³ In 2004, the region with the largest percentage increase in international tourist arrivals was Asia and the Pacific, with a 28% increase compared with 2003 (figure 4).⁶³

Increasing immigration, particularly from low-income countries, together with the ease and affordability of modern travel, have contributed to substantial increases in the number of travellers visiting friends and relatives in their country of origin.⁶⁴⁻⁶⁶ Travellers visiting friends and relatives now comprise a disproportionately high number of international travellers. First-generation immigrants constitute approximately 20% of the population of the USA, and visits to their friends and relatives accounted for approximately 40% of international air travel from the USA in 2002.⁶⁵ Similarly, whereas around two-thirds of UK residents who make trips abroad are travelling for tourist purposes, in 2003, visits to friends and relatives overtook business trips as the second most common reason for UK residents to travel abroad, and the proportion of such visits increased again in 2004.^{55,67} Travellers visiting friends and relatives are an increasing source of imported cholera cases. Studies have suggested that this group are less likely to seek travel health advice than other travellers.^{65,68} They are also likely to be at higher risk of contracting cholera, as are expatriates, because they may have closer contact with the local population and their associated accommodation, water sources, and food.^{64,66}

The continuing presence of emergency relief workers and military personnel in cholera endemic and epidemic areas are also likely to represent an important source of imported disease.¹⁶ These individuals tend to be in closer contact with the local population than other groups of travellers, and they are also likely to be in an environment where conditions are more suited to the transmission of cholera, such as contaminated water supplies and crowded living conditions after natural disasters, civil unrest, or war.¹⁶

The trend for increasing travel to endemic regions of the world is likely to produce an increasing risk for the importation of cholera. Greater assessment of the risk of disease within popular travel destinations, in combination with the new International Health Regulations that allow reverse tracking of the epidemiology of cases, may help in estimating the risk to travellers and in improving awareness of areas that currently under-report cholera. This will be valuable in better assessing the risk to travellers from countries that fail to report cholera, and may also help in the implementation of systems to reduce the risk to the indigenous population.⁶⁹

Actual cases of cholera among travellers are likely to be higher than recorded, because only the most severe cases of cholera tend to be reported.¹⁶ Milder cases may go

unrecognised and unreported, because symptoms are similar to other diarrhoeal diseases and do not always constitute a significant health problem. Additionally, the incubation period for cholera is relatively short, with disease manifesting suddenly between several hours and within 5 days after infection. Consequently, many travellers may experience disease while still abroad, and so cholera is not always imported to their country of origin.^{16,24} In many countries, even if health advice is sought, microbiological screening is not routinely undertaken.¹⁶ The overall risk for travellers to contract cholera is thought to be in the order of two to three cases per 1 million travellers.⁵⁶ However, in a study in which travellers returning with diarrhoea were routinely screened for *V. cholerae*, this figure rose substantially to approximately five cases per 100 000.^{24,56} Furthermore, among long-term travellers visiting areas where cholera outbreaks occur, the incidence may be as high as five per 1000 travellers.^{56,70}

It could be argued that any increase in imported cases of cholera in industrialised countries is not a major public-health problem: imported cases are unlikely to lead to outbreaks because of proper public-health and environmental management. Consideration should be given to the fact that imported cholera could also cause complications in specific high-risk groups of travellers, such as those with renal failure. The fact that the number of imported cases is increasing in some high-income countries is a substantial cause for concern, and this reflects the sustained increase in international travel and subsequent potential exposure to infectious diseases including cholera. Furthermore, it could be postulated that most high-income countries do not actively search for cholera when returning travellers report diarrhoeal problems post-travel, another factor that may lead to underestimation of the true scale of the problem.

Consequences of under-reporting of cholera

Many decisions concerning the prevention and control of cholera are based on surveillance reports. Under-reporting hinders provision of appropriate health advice to travellers and adequate interventions in at-risk indigenous populations, because health-care professionals and policymakers might underestimate the true risk and burden of cholera. Travellers may be better prepared if the risk of cholera was also assessed in terms of endemicity in addition to epidemics. Efforts to improve the accuracy and availability of information relating to the epidemiology of cholera will be crucial in ensuring that the individuals at risk are identified and that interventions are targeted appropriately.

Prevention of cholera

The prevention strategies regarding the avoidance of food and water-borne disease differ for indigenous populations and travellers, because most travellers, other than expatriates, do not live in the same conditions as the indigenous population during their stay (one

exception being travellers to endemic areas who want to experience the indigenous population's way of life). Nevertheless, the following basic principles are important for both groups: ensure satisfactory overall hygiene and sanitation, an adequate supply of safe drinking water, and effective food hygiene.^{4,16} When followed rigorously, the risk of contracting a sufficient inoculum of *V cholerae* to cause disease is low. Although prevention of cholera requires clean water supplies and appropriate sanitation facilities, the implementation of these improvements in low-income countries is often slow. Regions where such interventions have not yet been put in place are those at greatest risk of cholera epidemics.

Up to 50% of travellers experience travellers' diarrhoea, and not all these cases will be cholera.^{17,72} Strict adherence to preventive advice can protect against infection with other enteric pathogens that are transmitted via the same route as cholera. However, in practice, it is difficult for travellers to avoid all sources of potential contamination, particularly if they are living in close proximity to the local population, as well as being reliant on the local infrastructure for basic services such as food, water, and sanitation.^{64,66,71} Of note, within 72 h of their arrival, 98% of travellers to Sri Lanka or Kenya had failed to adhere to advice on what to eat and drink.⁷³

In terms of treatment, access to rehydration solution can be difficult in isolated areas, which might contribute to mortality after infection. Antimicrobial therapy can halve the duration of illness and help to reduce secondary transmission, particularly in settings where affected people are living in close proximity to one another. However, the use of antibiotic prophylaxis is not recommended as a preventive measure because it has a limited effect on the transmission of cholera, and antibiotic resistance remains an increasing problem.^{11,74,75}

Vaccination in the prevention of cholera

Production of the first injectable killed whole-cell vaccines began shortly after the causative agent was discovered in the 1880s.^{6,11} These vaccines were widely used by travellers in the early part of the 20th century when proof of vaccination against cholera was required by many countries.^{6,11,76} Side-effects, limited efficacy, cost, and the necessity for frequent booster injections, together with improvements in sanitation and the knowledge that vaccination did not prevent spread of disease, mean that these vaccines are no longer recommended for use.^{6,11,76}

Several newer vaccines against cholera are currently licensed in some countries. An oral, single-dose vaccine, CVD 103-HgR, has been prepared from a live, attenuated, genetically modified strain of cholera derived from the classical O1 strain. Protective efficacy of 80% was reported in a challenge study with *V cholerae* O1 El Tor Inaba undertaken in adult volunteers in the USA 3 months after vaccination.⁷⁷ However, this vaccine gave good efficacy against the *V cholerae* classical biotype, but only 65% protection against the *V cholerae* El Tor biotype, in a clinical

study in adult volunteers in the USA.⁷⁸ Additionally, results of a large field trial in Indonesia did not show convincing protection.⁷⁹ The manufacturer stopped production of this vaccine in 2004, and, although licensed, it is no longer available.²²

An inactivated oral vaccine, consisting of killed whole-cell *V cholerae* O1 of several strains (Inaba and Ogawa serotypes, classical, and El Tor biotypes) with purified recombinant cholera B subunit (WC/rBS), is currently the only cholera vaccine pre-qualified by WHO for the UN to purchase (Dukoral, SBL Vaccin AB, Stockholm, Sweden).⁸⁰ The vaccine can be self-administered as a drink with two doses generally given at least 1 week apart, with the last dose given at least 1 week before travel to a cholera risk area. Boosters can be given for continued protection after 2 years for adults and children over 6 years of age, and after 6 months for children aged 2–6 years. The WC/rBS vaccine has been shown to have few side-effects.⁸¹ Adverse events that have been recorded are mostly related to gastrointestinal symptoms, which are generally mild.⁸² Efficacy has been shown in clinical studies in Bangladesh and Peru, with a profile of 85% disease risk reduction within the first 6 months.^{83–86}

Furthermore, WC/rBS vaccine provides some cross-protection against enterotoxigenic *E coli* diarrhoea, which affects 30–50% of people travelling from high-income to low-income countries.^{71,72,87} Enterotoxigenic *E coli* strains produce two toxins, heat stable and heat labile, and can produce either or both of these toxins. Heat labile toxin has an 80% aminoacid similarity to cholera toxin, and the structural, functional, and immunological similarities between these toxins afford a mechanism that allows for the cross-protection seen.⁸⁸ Clinical studies in endemic areas and in those travelling to endemic areas have shown that vaccination with WC/rBS results in greater than 50% protective efficacy against enterotoxigenic *E coli* diarrhoea, regardless of toxin type.^{87,89} When only considering heat labile-producing strains of enterotoxigenic *E coli* (responsible for two-thirds of cases of enterotoxigenic *E coli* diarrhoea), the protective efficacy rose to 60% or more.^{87,89} Furthermore, disease manifestation in vaccinated individuals was generally milder.⁸⁷

A killed whole-cell *V cholerae* O1 vaccine, without recombinant B subunit, has been developed as a result of technology transfer. In a trial of more than 50 000 people, two doses of vaccine gave a protective efficacy of 66% during an outbreak of El Tor cholera that occurred 8–10 months after vaccination.⁹⁰ This vaccine (currently licensed in Vietnam) has been shown to be safe, immunogenic, and affordable for mass vaccination campaigns.^{91–93}

There are several live attenuated vaccines against cholera being developed. These include Peru-15, a vaccine candidate that is based on the *V cholerae* O1 El Tor strain. Safety and immunogenicity was established in a trial in Bangladesh, and protective efficacy of at least 62% was shown in a challenge study in North American

volunteers.^{94,95} Protective efficacy of another candidate vaccine based on the El Tor strain, *V cholerae* 638, has only been shown in a study in Cuban volunteers.⁹⁶ Additionally, live attenuated vaccines against more than one strain of cholera are in development.

Vaccination of indigenous populations

The administration of cholera vaccines as a public-health intervention in low-income countries has recently become feasible with the advent of an effective vaccine. Vaccination could be considered as an additional tool to combat cholera in low-income countries alongside established control measures. Importantly, a study in women and children in Bangladesh showed that killed oral cholera vaccines confer herd immunity, extending protection to non-vaccinated individuals, and thus strengthening the possible public-health benefit and impact of cholera vaccination.⁹⁷ WHO currently recommends pre-emptive use of cholera vaccination in certain endemic and epidemic situations, although clear guidelines have yet to be developed.⁹⁸

Mass vaccination has been shown to be effective in refugee camps. In Uganda, in October, 1997, 44 000 south Sudanese refugees were vaccinated with WC/rBS. Vaccine coverage was 83% and 76% for the first and second dose, respectively, and none of the vaccinated individuals presented with cholera during an epidemic that occurred a year later.^{99,100} In 2004, WHO organised a cholera vaccination campaign in refugee camps in Sudan, where cholera outbreaks occur frequently with high incidence from December to April. Vaccine coverage of 88–94% was achieved in two camps in south Darfur, Kalma and Mussei, in July and August, and no cases of cholera were reported from Sudan in 2004.^{21,101,102}

Mass vaccination campaigns with WC/rBS have also been successful in endemic regions. In Beira, Mozambique, a campaign was initiated before the rainy season, with which cholera outbreaks are often associated. Protective efficacy was shown in 78% of individuals who had received two doses of cholera vaccine, and importantly, this was the first study to target a population with a high prevalence of HIV, although the actual HIV prevalence was not specifically determined.¹⁰³ Many cholera-infected African populations have a high prevalence of HIV, which puts individuals at higher risk of contracting serious clinical disease.

Mass vaccination campaigns with live attenuated cholera vaccines have also been undertaken. For example, single-dose oral cholera vaccine CVD 103-HgR was administered to the population of Pohnpei Island, Micronesia, as part of control measures to limit the spread of a cholera outbreak. The efficacy of the vaccine was estimated at 79.2%, although the study was neither randomised nor blinded.¹⁰⁴ High vaccination coverage (79%) was achieved with a cost-effective, locally produced, two-dose, killed whole-cell cholera vaccine in 13 communes in Hue, Vietnam, in 1998.⁹³

Vaccination of travellers

Cholera is endemic in much of the developing world and travellers to countries reporting cholera should be advised of precautions to avoid infection. Travellers from high-income nations have no underlying immunity, and are consequently at risk of contracting cholera in these regions, even if no epidemics have been reported.

Protection of travellers to high-risk areas through administration of cholera vaccine reduces the risk of importing disease, and the risk of travellers contracting cholera while abroad. Certain groups of travellers who are more likely to experience severe diseases may be particularly recommended to receive cholera vaccine. These include long-term travellers to endemic areas and those with underlying medical disorders that could be aggravated by diarrhoea. The risk to travellers who are taking medication that lowers gastric acidity should also be considered. An increased risk of infection is associated with travellers likely to be in close contact with the local population (including travellers visiting friends and relatives, and expatriates), emergency relief workers, health-care and military personnel, and travellers to areas with a high risk of infection or with insufficient access to medical facilities, such as backpackers. It is important to assess the risk to the individual traveller should they be exposed to cholera, and to consider vaccination if appropriate.

Enterotoxigenic *E coli* diarrhoea is common in cholera-endemic regions, and therefore a vaccine protecting against both diseases has increased health benefits for the traveller (up to 50% of people travelling from a high-income to a low-income country have travellers' diarrhoea).^{1,71,72} WC/rBS vaccine is currently the only cholera vaccine that has been shown to give protective efficacy against a proportion of enterotoxigenic *E coli* diarrhoea caused by heat labile-producing strains of enterotoxigenic *E coli*.^{89,105}

WHO International Travel and Health guidelines recommend that oral cholera vaccines can be administered selectively to travellers, and in particular to those at increased risk of exposure, including emergency relief and health workers deployed to refugee situations.⁴ Oral cholera vaccines are an option for those travelling to high-risk endemic areas. However, the guidelines also state that cholera vaccination is not necessary for most travellers. This recommendation has been recently challenged, with the suggestion that all precautions should be taken to reduce morbidity and mortality, and that no one should be deterred from vaccination.¹⁰⁶

Vaccination in emergency situations

In a recent update on the potential use of oral cholera vaccines, WHO stated that their pre-emptive use during an outbreak crisis has been accepted.²² Cholera vaccination should be undertaken in the context of a multidisciplinary approach, taking broader public-health priorities into consideration.

For more information on WHO International Travel and Health guidelines see <http://www.who.int/ith/en/>

Conclusions

Cholera is under-reported in indigenous populations and travellers, for various reasons. For example, cholera may be more prevalent in popular travel destinations, such as the Indian subcontinent and Thailand, than is generally believed. Cholera is also on the increase. With a rise in global travel to high-risk areas, including substantial increases in the number of travellers visiting friends and relatives in their country of origin, more travellers are at risk of contracting cholera than previously thought. These changing travel trends could potentially lead to an increase in imported cases of cholera if appropriate travel health advice is not provided. Furthermore, civil unrest and the increasing incidence of natural disasters as a result of climate change may place more emergency relief workers and military personnel at risk of infection.

Under-reporting of cholera has serious implications for the prevention and control of cholera. The true extent of the problem needs to be evident before cholera can take its appropriate place on the list of health priorities, particularly in low-income countries. Indeed, underestimation of the risk of cholera impedes the implementation of strategies to combat the disease.

Accurate data on disease incidence is also needed to help travel health-care practitioners assess the risk of infection, particularly for those more likely to experience severe disease and for those travelling to high-risk areas and likely to be in close proximity to the indigenous population. After a comprehensive travel health-risk assessment, consideration of the appropriate administration of cholera vaccine should be made to reduce the potential of importation of disease and subsequent public-health concerns, as well as protecting the individual.

Cholera is unlikely to ever be eradicated, and this fact emphasises the importance of the provision of adequate methods of prevention, preparedness, and that control

Search strategy and selection criteria

A weekly search of relevant websites was carried out in 2004 to identify reports of cholera that were not reported to WHO. English, Swedish, and German language reports were included. Unconfirmed cases and cases caused by *V cholerae* serotypes other than O1 and O139 were excluded. Sources included PubMed, Armed Forces Research Institute of Medical Sciences, AllAfrica, *Canada Communicable Disease Report*, *Communicable Disease Report Weekly*, Centers for Disease Control and Prevention, *Eurosurveillance*, Global Infectious Disease and Epidemiology Network, UK Health Protection Agency, IOL FrontPage, United Nations Integrated Regional Information Networks, Newsbug.net, ProMED-mail, Reuters, WHO, and Xinhuanet. Where appropriate, the following search terms were used: "cholera", "epidemiology", "outbreak", "imported cases", "V cholerae O1", "V cholerae O139", and "severe diarrhoea".

measures are in place. These methods include the provision of appropriate health care, health education, adequate standards of sanitation and food hygiene, and the availability of vaccination and effective immunisation programmes. Mass vaccination against cholera is a relatively new strategy that could be used in conjunction with efforts to improve sanitation in certain high-risk populations; however, identification of these populations requires effective disease surveillance. In conclusion, a multifactorial approach will be required to mitigate the threat of this public-health problem.

Conflicts of interest

JNZ has been reimbursed by several manufacturers of vaccines including Baxter AG, GlaxoSmithKline, Sanofi Pasteur, Chiron Evans, and Wyeth for attending conferences, for doing vaccine studies, and for running educational programmes, and has received unrestricted educational grants. JNZ is also a consultant in travel medicine to the British Airways travel clinics. LR undertakes vaccine trials for GlaxoSmithKline and Aventis-Pasteur MSD, and has been part of the SBL Vaccin AB advisory board for Dukoral. AF declares no conflicts of interest.

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