Cholera's western front

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See Leading Edge
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The cholera epidemics of the 19th century forged the way for the revolution in sanitation and the provision of safe sources of public water, which are the hallmark of developed countries. Nevertheless, more than 1 billion people, including much of the Haitian population, have little access to safe sources of water, and hence remain vulnerable to cholera epidemics.[1]

Before the current epidemic, cholera most recently occurred in the western hemisphere in the early 1990s. After being absent from the region for more than a century, cholera reappeared in Peru in January, 1991. The first patients were in a coastal village 80 km north of Lima. By the end of 1991, more than 390 000 cholera cases and more than 4000 deaths had occurred in 16 countries. Although the ferocity of the outbreak in the first year was unmatched, cholera remained endemic in the hemisphere for 10 years, with the last reported death in 2001. From a worldwide perspective, the 1990s epidemic in the western hemisphere was only one part of an ongoing pandemic of cholera, which began in Indonesia in 1961. This pandemic is the seventh that has occurred in the past 200 years; the causative organism is an El Tor biotype of *Vibrio cholerae* serogroup O1. This biotype has been so successful from an evolutionary perspective that it has replaced the previous biotype in circulation. Pulse-field gel electrophoresis at the US Centers for Disease Control and Prevention indicates that the epidemic strain of *V cholerae* in Haiti is similar to the strains of seventh pandemic El Tor in south Asia.[2] After the 1991 outbreak, the public health infrastructure was strengthened in many Latin American and Caribbean countries. However, access to safe water remains uneven in the hemisphere, most notably in Haiti. In 2008, only 12% of Haitians received piped treated water, and only 17% had access to adequate sanitation.[3] The earthquake in January destroyed the already fragile infrastructure in Haiti, and left more than 1 million people living in makeshift encampments, mainly in Port-au-Prince. Concern for possible outbreaks of diarrhoea was high after the earthquake, but no immediate event occurred.

On Oct 19, 2010, an unusually high number of patients (mostly aged older than 5 years) with acute watery diarrhoea were identified in the Artibonite and Centre departments—densely settled rural areas, which were not heavily affected by the earthquake. The National Public Health Laboratory in Haiti quickly isolated *V cholerae* O1 from stool specimens from patients in the affected area. Cholera has since spread rapidly across the country. As of Nov 17, 2010, 18 382 hospital admissions, and 1110 deaths due to cholera have been reported (figure 1).[5] Cases have

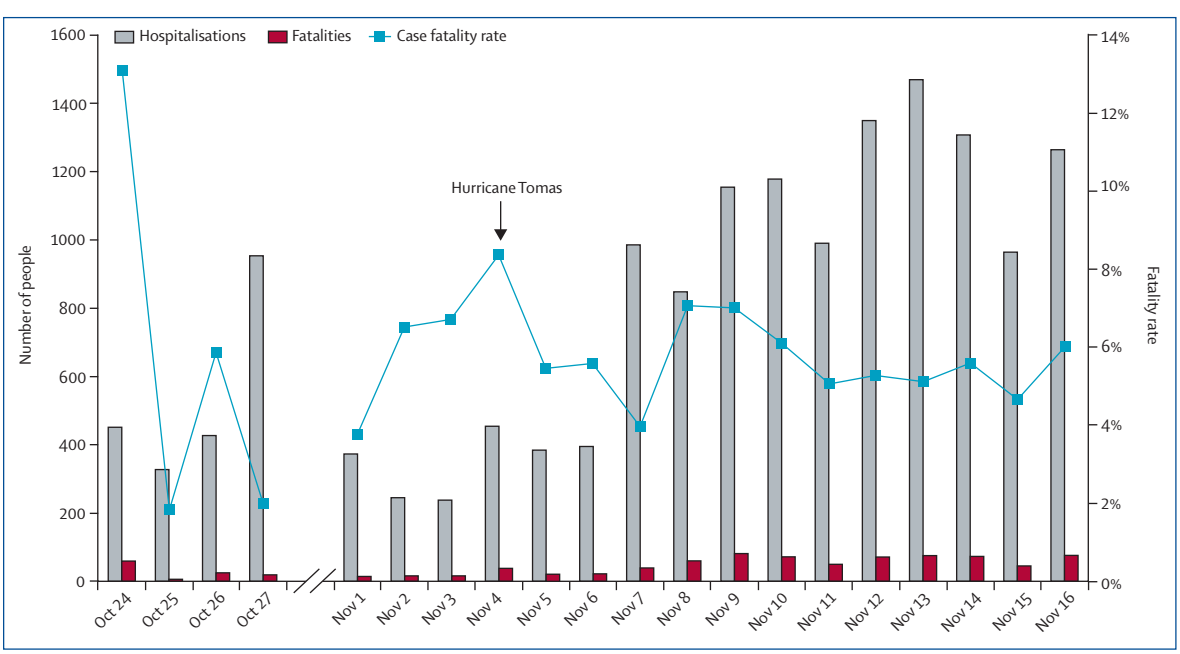

Figure 1: **Epidemic curve for Haiti cholera outbreak[4]**

now been confirmed in seven of Haiti's ten departments, including 953 cases within Port-au-Prince. Single cases have also been reported in the neighbouring Dominican Republic and in Florida, USA. Treatment, prevention, and control measures are underway in Haiti, and have focused on disseminating educational messages about safe water and sanitation practices, and about the use of oral rehydration solution, an inexpensive and highly effective treatment. 32 treatment centres for cholera have been established within health-care institutions and in freestanding locations.

A case fatality rate of less than 1% has long been used as the benchmark to assess the effectiveness of such cholera interventions; with adequate fluid management, rates of case fatality for cholera can be reliably reduced to this low level. At the International Centre for Diarrhoeal Disease Research in Dhaka, Bangladesh (ICDDR,B), which played a crucial part in the development of oral rehydration solution and has extensive experience of managing patients with severe diarrhoea, case fatality rates are less than 0·2%.[6,7] In the early stages of the epidemic in Haiti, the rate of case fatality for cholera remains at 6%.

The history of cholera outbreaks within the past 10 years shows that case fatality rates of 1% or less are rarely achieved in outbreak settings (figure 2). In the 2008–09 cholera outbreak in Zimbabwe, which involved nearly 100 000 people, the case fatality rate was 4·3%. In the 2006–07 Angola outbreak, the rate was 4%. Of the African nations with cholera, only South Africa, which has a more developed health infrastructure, was able to achieve rates of less than 1% in its 2000–01 outbreak. In the western hemisphere, case fatality rates reached 5% or more in the weeks after the emergence of cholera in Peru in 1991. Although an overall case fatality rate of 0·34% was achieved, rates remained as high as 3% in the less developed mountainous and jungle areas of Peru throughout the epidemic.

There are biological and organisational challenges to the achievement of low rates of case fatality during a cholera outbreak. Most importantly, the difficulties of providing medical care during a complex emergency must be overcome. Infection with the organism yields protective immunity, and hence cholera can cause more explosive outbreaks in a naive population than in

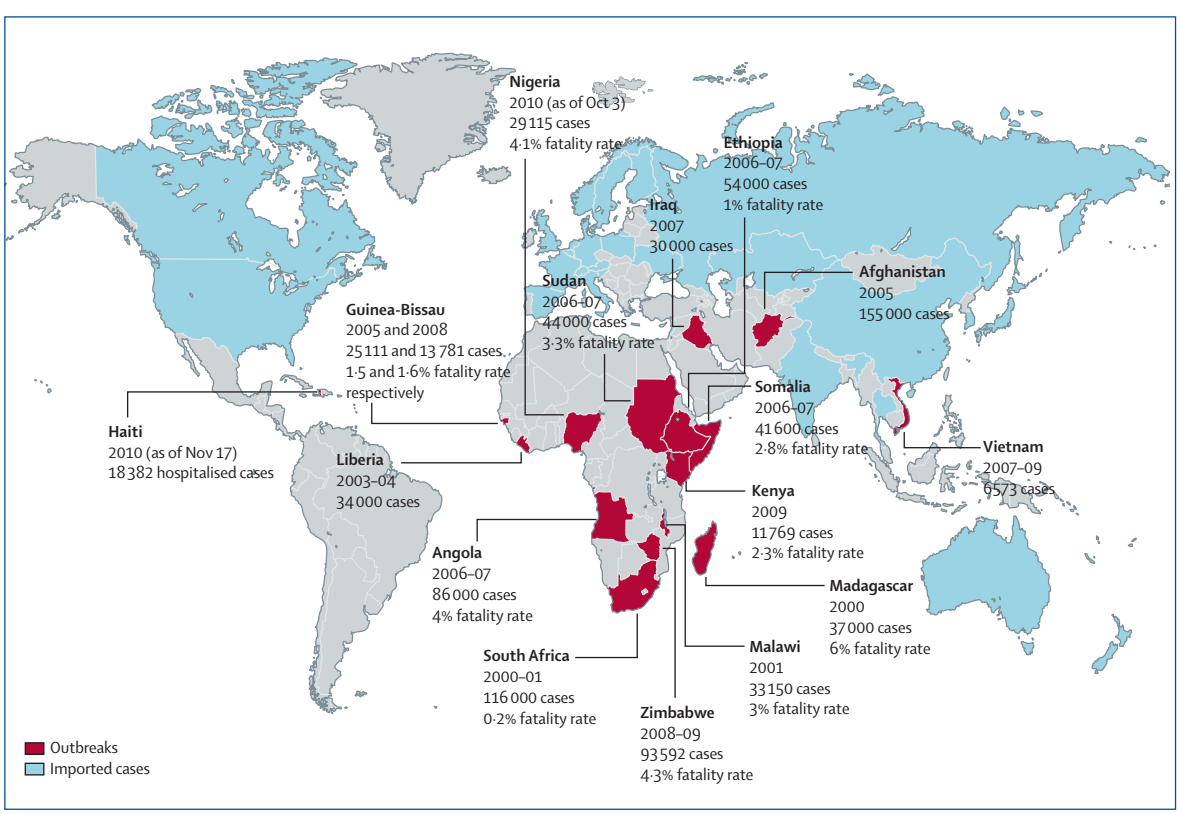

Figure 2: **Major outbreaks of cholera since 2000**
Selected outbreaks in red, with associated case fatality rates (where reported). Countries with imported cases between 2004 and 2009 are in blue.

a population living in an area that is cholera endemic, such as in south Asia. Host genetic factors (including blood group O) predispose individuals to severe cholera, and differ in prevalence between populations in endemic and non-endemic regions.

Rehydration is the essence of cholera treatment. Because of the rapid losses of fluid seen in cholera, achieving optimum fluid management can be a challenge for health-care providers who are unfamiliar with the disease. Death might occur because the initial status of dehydration is underestimated or because ongoing fluid losses are underappreciated. Therefore optimum case management requires that efficient triage be in place, and that patients be frequently monitored. For patients presenting with severe dehydration, isotonic fluids (preferably lactated Ringer's solution) should be given as quickly as possible, often through several sites of intravenous access, until an easily detectable pulse is restored. The fluid deficit that remains should be replaced within the first 3 h after presentation, and ongoing fluid losses need to be factored in. Patients with severe cholera need an average of 200 mL per kg of isotonic fluids in the first 24 h of therapy, but this amount might range from 100 mL per kg to more than 350 mL per kg.[8] Patients without severe dehydration can usually be successfully treated with oral rehydration solution, which prevents complications of unnecessary intravenous therapy, and also conserves resources for more severe cases.

Several key resources outlining the appropriate management of patients with cholera are freely available.[8–10] These resources range from simple pocket-cards to detailed publications about the management of diarrhoeal illness and its complications. The Cholera Outbreak Training and Shigellosis (COTS) Program deserves special mention because it outlines a comprehensive approach to the response to an epidemic of diarrhoea, including information in Haitian Creole.[10] To achieve less than 1% case fatality, health-care workers responding to cholera outbreaks should be familiar with the assessment of dehydration, patients' triage, and rapid oral and intravenous rehydration strategies outlined by these publications. Education of health-care providers about rehydration strategies has been an important focus of response efforts in Haiti. As such, the ICDDR, B is working with the Haitian Ministry of Health on a training of the trainers (TOTS) programme.

In addition to the challenges associated with fluid management, there are many misconceptions about the appropriate use of antibiotics during cholera outbreaks. Antibiotics for cholera shorten the course of diarrhoeal illness and reduce the volume of diarrhoeal stool output by up to 50%.[11,12] Antibiotics do not improve mortality from cholera under circumstances of optimum fluid management. However, in an epidemic, antibiotics save lives because they result in the quicker resolution of illness and the more rapid discharge of patients, both of which are essential for making resources available in an outbreak setting. Antibiotics also reduce the duration of shedding of infectious organisms in the stool from several days to about 1 day, which has substantial public health implications.[13] During an epidemic, antibiotics should therefore be given to all hospitalised patients as soon as possible. The current strain in circulation in Haiti is susceptible to doxycycline and azithromycin and resistant to nalidixic acid, with reduced susceptibility to ciprofloxacin.[2] On the basis of past experience, these results suggest that ciprofloxacin will probably be less effective against this strain.[11] The table shows appropriate antibiotic choices for the management of cholera in Haiti. Antibiotics are not indicated for mass chemoprophylaxis against cholera.

Although access to safe drinking water and adequate sanitation systems are essential to control cholera, these solutions are for long-term implementation. In the midst of an outbreak, point-of-use water purification should be used. Building latrines is a high priority; pit latrines should be located at least 30 m from any groundwater source. Educational messages

	Adult dose	Paediatric dose	Comments
Preferred antibiotics			
Doxycycline	300 mg single dose	4–6 mg/kg single dose	Resistance to tetracyclines has emerged during previous cholera epidemics. Resistance patterns should be monitored. Contraindicated in pregnant women. Not recommended in children younger than 9 years (teeth staining)
Azithromycin	1 g single dose	20 mg/kg single dose	Preferred in paediatric population
Alternative antibiotics			
Tetracycline	500 mg every 6 h for 3 days	50 mg/kg per day divided every 6 h for 3 days	Not recommended in children younger than 9 years (teeth staining)
Erythromycin	250 mg every 6 h for 3 days	40 mg/kg per day divided every 6 h for 3 days	..

Table: **Antibiotic choices for management of cholera in Haiti**

about hand washing with soap, safe handling of food, and safe funeral practices should be shared with the community. In hospital settings, cot disinfection with 0·05% bleach solutions can prevent nosocomial spread of disease.

For many years, concern has existed that cholera vaccination during epidemics might detract from other control measures, such as case management, treatment of drinking water, and sanitation measures. However, several developments have occurred, which are changing thoughts about cholera vaccination. A reanalysis of a large field trial in Bangladesh showed that oral cholera vaccines confer significant herd immunity; vaccinating more than 51% of the population in a geographic area led to a substantial reduction in cholera rates in individuals who had not themselves received the vaccine (from 7/1000 people to <1·5/1000).[14] An analysis of oral vaccination that included this herd-immunity effect showed that vaccination in various endemic settings was a cost-effective measure, likely to compare favourably with water and sanitation interventions.[15] This cost-effectiveness model assumed a case fatality rate of 1%. Experience from the past decade indicates that case fatality rates during cholera outbreaks are generally sustained above 5%, suggesting that the potential cost–benefit ratio of vaccination in such settings could be increased. Furthermore, oral cholera vaccines are now being produced in India and Vietnam at substantially lower costs.

Earlier this year, WHO changed its position paper on cholera vaccination in response to these data.[16] The use of cholera vaccines is now recommended in areas where the disease is endemic, and should be considered in areas that are at risk for outbreaks, a strategy known as pre-emptive vaccination. Pre-emptive vaccination requires a substantial stockpile of vaccine that is presently unavailable. The value of reactive vaccination to halt an ongoing epidemic is less clear. However, with the capacity to produce cholera vaccines that are lower in cost, there is now an opportunity to develop supplies of cholera vaccine that are sufficient to assess and to implement vaccination during complex emergencies and outbreaks, as in Haiti.

Because of cholera, the public health landscape of the western hemisphere has changed suddenly and dramatically. Spread of the disease beyond the borders of Haiti seems almost certain, and the organism might re-establish in the region for years to come. Recently, much attention has focused on the potential source of this outbreak strain. Although the answer to this question might or might not come, history has shown that cholera will eventually find its way to places where societal infrastructure has broken down. In the short term, efforts will continue to focus on education, case management, and measures of disease prevention, with the aim of reducing case fatality rates closer to the desired benchmark. In the long term, substantial improvements in water quality and sanitation will be needed for Haiti before reliable interruption of cholera transmission can occur. The dark shadow of cholera has provided the impetus for remarkable change in the past. Hopefully, this latest threat for the people of Haiti might represent a turning point in their quest for access to the most basic of human needs—safe water.

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Zoledronic acid in myeloma: MRC Myeloma IX

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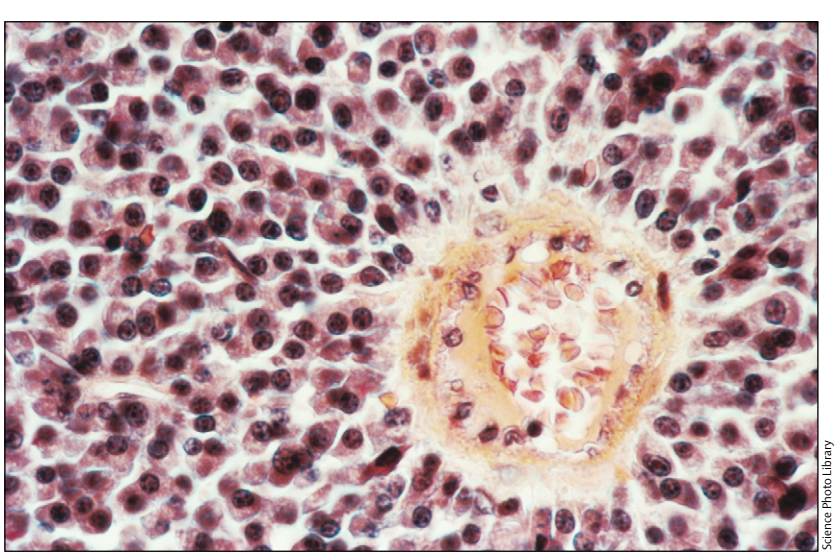
Osteolytic bone lesions are the main cause of morbidity in multiple myeloma, and occur in about 70% of patients at initial diagnosis of the myeloma.[1] In patients with newly diagnosed disease presenting with evidence of bone disease, prophylactic bisphosphonates (clodronic, pamidronic, or zoledronic acids) given from initial diagnosis reduce the proportion of patients who develop future skeletal-related events, and extend the time to develop a skeletal-related event.[2-4] Consequently, bisphosphonates are recommended for all patients with evidence of myeloma-related bone disease.[5-7]

In *The Lancet*, Gareth Morgan and colleagues[8] present an important randomised trial (MRC Myeloma IX), in which they compared two disparate bisphosphonates, oral clodronic acid versus intravenous zoledronic acid, in nearly 2000 patients with newly diagnosed myeloma. Treatment with zoledronic acid was associated with a significant reduction in the proportion of patients with skeletal-related events, a secondary endpoint (27% *vs* 35% with clodronic acid), and slightly increased median progression-free survival by 2·0 months. But most remarkably, median overall survival was significantly improved by 5·5 months with zoledronic acid compared with clodronic acid, and this finding cannot be explained by a beneficial effect on skeletal-related events alone. Morgan and colleagues postulate that this finding strengthens the argument that zoledronic acid might have direct antimyeloma properties in addition to its antiresorptive effects on bone.

Does the beneficial effect of zoledronic acid on overall survival compared with clodronic acid have a scientific explanation? After all, clodronic acid, despite having an osteoclast inhibitory effect 1000 fold less potent than that of zoledronic acid,[9] and saddled with the disadvantages of poor oral bioavailability and gastrointestinal side-effects inherent with oral bisphosphonates, achieved median progression-free survival only 2 months shorter than that with zoledronic acid. The answer is yes. Although clodronic acid and zoledronic acid are both derivatives of inorganic pyrophosphate (bisphosphonates), they are different in terms of structure and mechanism of action. Clodronic acid belongs to a subgroup of non-nitrogen-containing bisphosphonates that act by the generation of non-hydrolysable ATP analogues toxic to osteoclasts.[6,9] By contrast, nitrogen-containing bisphosphonates, such as pamidronic acid and zoledronic acid, inhibit the enzyme farnesyl pyrophosphate synthase, which eventually prevents prenylation of several regulatory proteins, leading to osteoclast apoptosis.[10] Zoledronic acid might also



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Cancerous myeloma cells in darker purple