Cholera - The Grim Reality of Under-development

Durrheim, DN
MB, ChB, DTM&H, DCH, FACTM, MPH &TM
Communicable Disease Control, Mpumalanga Department of Health, Nelspruit

Ogunbanjo, GA
MB, BS, MFGP (SA), MFamMed (MEDUNSA)
Department of Family Medicine & Primary Health Care, Medical University of Southern Africa (MEDUNSA), Pretoria

Blumberg, L
MB, BCh, DTM&H, DOH, DCH
Dept. of Clinical Microbiology & Infectious Diseases, South African Institute for Medical Research & University of the Witwatersrand, Johannesburg

Keddy, KH
BSc (Med), MB BCh, DTM&H, FRCPath (SA), MMed
Dept. of Clinical Microbiology & Infectious Diseases, South African Institute for Medical Research & University of the Witwatersrand, Johannesburg

Correspondence to:
Prof. Dave N. Durrheim
Communicable Disease Control
Mpumalanga Department of Health
P Bag X 11285
Nelspruit, 1200
E-mail: daved@social.mpu.gov.za

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Abstract

Cholera is a severe diarrhoeal illness caused by certain strains of Vibrio cholerae, which can lead rapidly to dehydration and death. Communities dependent on water contaminated with human faeces and those with poor sanitation are very vulnerable to cholera epidemics. Although the Vibrio cholerae O1 El Tor strain presently circulating in southern Africa is multi-drug resistant and currently available vaccines offer inadequate protection, cholera can be pre-vented by simple cost-effective measures, including chlorination or sustained boiling of drinking water. The key to cholera management is aggressive fluid replacement with the correct fluids. The latter strategy is so effective that a cholera death may be viewed as a health system failure deserving formal review. The only sustainable solution to the scourge of cholera is fundamental economic and social development with the provision of safe water and adequate sanitation for all communities.

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Introduction

Although Robert Koch only described the microbiological cause of cholera in 1884, cholera is a disease of antiquity. Up to 150 years ago its origin and means of transmission were unknown and "miasmas", or bad vapours, were usually blamed. John Snow, the founder of modern epidemiology, demonstrated the importance of water-born transmission of cholera in the mid 1850's.[1] Although it is unlikely that his dramatic act of removing the Broad Street pump handle had any direct public health effect, this bold action following careful epidemiological study set the precedent for rapid thorough field investigation of all suspected cholera outbreaks as the basis for prompt corrective action.[2]

Six major pandemics of the Classical biotype of Vibrio cholerae O1 were described between 1817 and 1923. The Hajj, the annual Muslim pilgrimage to Mecca, played a major role in disseminating cholera in pandemics four, five and six. Then in 1961 cholera appeared in Indonesia and spread rapidly across Asia and into Africa. This epidemic was caused by the El Tor biotype of V. cholerae 01. Thirty years later, in 1991, another El Tor strain appeared in Peru and rapidly spread through Latin America. In 1992, a new strain (O139 "Bengal") of V. cholerae emerged in India and caused a major epidemic in the Indian sub-continent.

Humans are the only vertebrate host of the Gram-negative, comma-shaped Vibrios responsible for cholera. These bacteria are well adapted to life in fresh and brackish water, and are highly motile. They are able to metabolise a wide range of nutrients and grow most rapidly in a neutral or basic pH, but are susceptible to desiccation, sunlight, and acid.

There are important differences between the Classical and El Tor strains. The El Tor strains are more likely to produce inapparent infections, in fact serological surveys have demonstrated that during a waterborne El Tor epidemic the actual number of infections exceeds reported clinical cases by at least 10-fold.[3] In addition the El Tor strain is able to persist for longer in the environment, multiplies more rapidly in food, and evokes less complete immunity. Following an infection with the El Tor strain, approximately 60-70% protection is provided against subsequent infection with either the El Tor or Classical biotype. One of the perplexing questions regarding cholera is the ability of the organisms to persist in rivers and estuaries contaminated with human faeces for periods extending to a number of years. The best examples of this conundrum are found along the US Gulf Coast and some rivers of north-eastern Australia. This persistence is believed to be due to two factors, namely the bacteria's ability to coexist with plankton and to enter a dormant phase.

Recent experiences with cholera in South Africa

The rural eastern provinces of South Africa are very vulnerable to cholera outbreaks.[4] Over 25 000 cases of cholera were bacteriologically proven during the South African cholera epidemic that lasted from 1980 to 1987, following the detection of the first case at Shongwe Hospital, in Mpumalanga Province on 2 October 1980. The case fatality rate was 1.4% and most patients were rural inhabitants of eastern South Africa, predominantly KwaZulu-Natal, Mpumalanga, Northern Province and the Eastern Cape Province, where there is an annual rainfall of more than 600 mm. Cholera then appeared to vanish from South Africa.

A large El Tor epidemic flared up in southern Mozambique during August 1997 with more than 10 000 cases by the end of that year. In February 1998 a young Mozambican male was the index case of a localised outbreak in Shongwe District in Mpumalanga's Lowveld Region on a banana plantation and the neighbouring rural village, Phiva. A sensitive surveillance system, rapid appropriate public health response and Divine providence saw this outbreak contained with only 20 proven cholera cases.[5]

During 1998 and 1999 there were a small number of sporadic cholera cases due to migration from Mozambique. These rural patients in Mpumalanga and urban cases in Johannesburg, Secunda and Durban were adequately managed and spread contained. Then in early 2000, severe flooding saw the destruction of already tenuous water supply and sanitation in the Mpumalanga Province Lowveld Region. The area was placed on high alert for potential cholera outbreaks. El Tor cholera was again imported onto a banana plantation and Albertsnek Village that adjoins Mozambique. This outbreak was also contained, and there were only 21 proven cholera cases and no deaths.

However in August 2000 the vulnerability of rural South Africa to V. cholerae was accentuated by the massive El Tor outbreak in the Empangeni area of KwaZulu-Natal Province. This spread to the Eshowe and Ulundi areas in the north and Port Shepstone in the south and by the end of December 2000, more than 12000 cholera cases had been confirmed by the health services with a death toll of 52 cases.

Important epidemiological features of cholera

Vibrio cholerae O1, El Tor biotype causes epidemic, life-threatening diarrhoea world-wide, with a high proportion of asymptomatic cases and carriers compared to the Classic biotype.[6] Most large cholera outbreaks occur in environments of extreme poverty. During recent South African outbreaks, surface water contamination proved to be an effective means for cholera transmission in an environment where clean water and adequate sanitation are often unavailable.

In developing settings, where waterborne spread is responsible for large epidemics, cholera can persist for many years, decreasing markedly during the winter months and then escalating during summer. Cholera may then "disappear" possibly due to the depletion of susceptibles, but then recurs after a number of years, presumably because the organism has found an environmental niche, most likely in synergism with plankton.[7] The hypothesised role of phytoplankton and zooplankton as reservoirs of V. cholerae in brackish and estuarine water has been supported by PCR findings demonstrating V. cholerae O1 for longer than two years in a cyanobacterium, Anabaena sp.[8] Although a rare long-term carrier state has been described in humans, it does not appear to play an important role in continued transmission.

In addition to the waterborne route, contaminated food has also been implicated in the transmission of cholera. Street vendors have served as a source of contaminated food, beverage, seafood, leftover rice, and contaminated fruit and vegetables.[9] Bathing in contaminated surface water has also served as an effective means of transmission of El Tor cholera.[10]

Cholera disease follows ingestion of food or water contaminated with an infectious dose of the causative organisms. For healthy individuals approximately 10^9 organisms are required to produce severe diarrhoea and this means that cholera is rarely transmitted directly from one person to another through casual social contact, without the intervening contamination of food or water. As Vibrios are exquisitely sensitive to acid, the stomach serves as an important barrier. Thus people with reduced gastric acid production e.g. following gastric surgery, antacid medication for ulcers, and very young and old patients, are at increased risk for severe disease. An interesting feature is the strong association of severe cholera with the "O" blood group.

Clinical presentation of cholera

The classical clinical picture associated with cholera infection is the acute onset of profound watery diarrhoea that may be accompanied by abdominal cramps but is typically not painful. The severity of the clinical picture is related to the number of organisms ingested. The usual incubation period is between 24 and 72 hours after ingestion of the infectious agent but may be as long as five days. Organisms that survive the acid assault in the stomach reach the small intestine and in this alkaline and bile-rich environment, they attach to mucosal cells and produce the cholera toxin. This is a protein enterotoxin that consists of an active A subunit of 240 amino acids, held within a pentamer ring of five B subunits, each of which has 103 amino acids. The toxin B subunits bind to receptors on the surface of intestinal mucosal cells. A portion of the A subunit then enters the cell and stimulates the production of cyclic AMP with resultant pumping out of chloride ions into the intestinal lumen and large quantities of potassium, bicarbonate, and water follow passively.

Cholera may be present in an asymptomatic state, as mild diarrhoea, or as typical full-blown disease. Initially the disease may present as watery, brown foul-smelling diarrhoea indistinguishable from the diarrhoea due to common pathogens, like E. coli. Then the typical odourless "rice water" stools will be passed, having the appearance of cloudy water with flecks of mucus. Fluid loss may be profound with up to 20 litres of fluid lost within a 24-hour period. Dehydration results in a dry mouth, absence of tears, increasing thirst, and loss of skin turgor. Continued loss leads to decreased blood pressure, and finally circulatory collapse. In the extreme state transient renal failure is not uncommon. Loss of bicarbonate leads to profound acidosis, with a blood pH below 7.0 and resultant vomiting. Loss of potassium leads to neuromuscular dysfunction, painful limb cramps, and ultimately to cardiac arrhythmia. As cholera infection is usually restricted to the small intestine, fever is rarely pronounced. It should be emphasised that in its extreme, cholera may be one of the most rapidly fatal diseases, with death within 2 –3 hours if no treatment is provided.

It is important to note that, to date, no increased severity has been described among persons infected with human immunodeficiency virus (HIV).

How to save the lives of infected patients?

There are few clinical situations where correct management can be so immediately rewarding and life saving than in treating cholera cases. Diarrhoea decreases after a few days of vigorous fluid therapy, and patients recover as soon as the fluid and electrolyte deficits are corrected. Rapid replacement of lost fluids and electrolytes with correct oral and intravenous solutions reduces mortality from 25 - 50% to less than 1%.

Most patients who present early only require adequate oral rehydration. This should preferably be started at home, and emphasis should be placed on preparing and using oral rehydration therapy in community health promotion strategies. Although the search for an ideal oral rehydration continues, sugar-salt solution is adequate for the majority of patients who are only mildly dehydrated.[11] Adding citrus juice to the sugar-salt solution improves taste, adds potassium and the acid kills bacteria.[12]

Where patients are severely dehydrated it is inappropriate to rely on oral rehydration and intravenous fluid replacement should be immediately initiated. Large volumes are required and the usual rule-of-thumb is reflected in Table I.

Thereafter careful monitoring of fluid status, urea and electrolytes, and direct faecal fluid loss, will dictate the maintenance rehydration rate. As enormous volumes of fluid may be needed it is essential to administer the correct rehydration fluids. For infants and children under 12 years the recommended rehydration fluid is **half-strength Darrow's solution with 5% glucose** while **Ringer's lactate with 5% glucose** is appropriate for older children and adults.[13] Ideally patients with cholera should be nursed in a "cholera-cot", however these are not generally available in South Africa. Experience with rectal placement of large bore Foley's catheters for monitoring faecal fluid loss has proven promising and infection control may also be simplified by this method. When the catheter begins to block, it is time for it to be removed.

It is fitting to caution that in certain settings case-fatality rates have exceeded 15% on average during an outbreak and even reached 48% in a single 24-hour period.[14] Factors contributing to high fatality rates serve as a warning to South African family practitioners. These include: a slow rate of rehydration, inadequate use of oral rehydration therapy, use of inappropriate intravenous fluids and inadequate experience of health workers. In South Africa, a cholera death should be considered a sentinel event deserving careful investigation to ensure that no remedial action of the health system is necessary.[15]

Health workers are rarely infected in health care settings and the risk of nosocomial infection can be further reduced by careful practice of standard and contact infection control precautions.[16] Particular emphasis should be placed on treating cholera patients in a separate "cholera" ward, while ensuring hand-washing, appropriate use of protective clothing, especially gloves and apron, and safe disposal of faeces.

Table I: ***Intravenous fluid replacement in cholera regimen***

Age	Intravenous fluid replacement
Patients aged 1 year and older	**100ml/kg in 3 hours** i.e. first **1/2** hour - 30ml/kg and remaining **2 1/2** hours -70ml/kg. Thereafter fluid replacement should equal measured stool volume plus normal daily requirements.
Patients aged less than 1 year	**100ml/kg IV in 6 hours** i.e. first **1** hour - 30ml/kg and remaining **5** hours -70ml/kg. Thereafter fluid replacement should equal measured stool volume plus normal daily requirements.

What is the role of antibiotics?

The role of antibiotics is limited in cholera control and patient management. Widespread antibiotic use has hastened the emergence of drug resistance and the El Tor strains currently circulating in southern Africa have a phenomenal resistance profile.[17,18] Only the quinolones remain effective against local cholera organisms. Thus although antibiotics may reduce the severity and duration of symptoms, their role remains adjunctive only and they cannot replace good rehydration therapy. Antibiotics have not been shown to reduce mortality, although they may reduce morbidity due to the disease.[19,20] As the disease is more likely to be maintained in the community by asymptomatic carriers, rather than the severely ill, antibiotics will probably make little difference to the course of the epidemic. Where a hospitalised adult patient is critical, a single dose (1 gram) of oral **ciprofloxacin** may be administered.[21]

Mass chemoprophylaxis has not succeeded in limiting the spread of cholera and cannot be recommended as it may fuel the development of resistance.[22] The ineffectiveness of this

strategy probably stems from the epidemic's ability to spread faster than the health service response, the short lasting effect of chemoprophylaxis and the necessity of all community members to be treated simul-taneously. It is debatable whether selective treatment of healthy household members of cholera patients may be beneficial.[23]

What is the role of the laboratory?

Of 193 recognised "O" serogroups of V. cholerae only O1 and O139 cause epidemics.[24] Although non-O1 infection can cause watery diarrhoea this is usually mild and does not have the same potential for epidemic spread.[25] It is thus important to determine the serogroup when cholera is diagnosed as it has major implications for control. In vulnerable areas, particularly during epidemics, rectal swabs should be collected from people with watery diarrhoea and transported in Cary-Blair transport medium to a suitably equipped laboratory. This alkaline medium allows the organisms to survive and grow, is extremely stable and can be kept at room temperature (25°C) for over a year.

In the laboratory V. cholerae grows well on several standard bacteriologic media. Efficient isolation however depends on the use of selective media that suppress growth of other bacterial species, while permitting V. cholerae to grow. Thiosulfate–citrate-bile salts-sucrose (TCBS) agar is the most widely used selective growth medium, although normal blood agar will suffice. When there is growth, it is important to test the suspicious colonies further with diagnostic antiserum for the presence of O1 antigen. Colonies that autoagglutinate in normal saline, before the antiserum is added, may need to be re-subcultured onto blood agar or boiled to remove any non-specific characteristics. The organism grows extremely rapidly, and colonies may be seen on the blood agar plate after only six hours.

In areas where resources are limited, it is not necessary to expend scarce funds confirming scores of cases from the same area during an epidemic. The laboratory is particularly useful in confirming the beginning of the epidemic in a specific area, for characterising the organism particularly its antibiotic sensitivity, assisting in the epidemiological investigation of source, transmission routes and spread, and establishing that the epidemic is over. Recent developments in the field of molecular epidemiology allow subtyping of El Tor Vibrios, and this information may be used to determine the geographical source of infecting strains.

How to contain cholera outbreaks?

The key to controlling epidemic cholera is prompt interruption of transmission so that the causative organism does not infect additional human hosts. Effective containment begins with thorough preparation for a potential outbreak. The community should be made aware that they are at risk of cholera and should have an appreciation of the potential severity of the disease. They should be well informed on how to make water safe. This could either be by boiling water at a rolling boil for 3 minutes, or adding domestic bleach – a capful to 20-25 litres of water that has been filtered through clean cloth or linen, mixed well and allowing to stand for a minimum of 4 hours. In addition it is essential that community members know how to respond if they develop diarrhoea. The importance of immediate oral rehydration with sugar-salt solution while in transit to consult their family practitioner or clinic is demanded by the rapidly dehydrating nature of the disease.

Early detection and correct response to cases will only be guaranteed if there is a high index of suspicion amongst clinicians and nurses, and sufficient stocks of rehydration supplies are available. In addition a simple surveillance system for detecting increases in diarrhoea cases and immediate notification of suspected cases must exist, and correct specimens should immediately be submitted from suspected patients on the correct media to a well-prepared laboratory. The role of rapid field investigation in response to suspected cholera cases cannot be overemphasised.[26] Experience from rural Tonga and Shongwe districts in Mpumalanga Province indicates that prompt community follow up of each suspected cholera case by a multi-skilled team, including a clinician or communicable disease control nurse, environmental health officer and health promoters, can effectively prevent the further spread of cholera in high-risk areas.[5]

Cholera was the first disease for which modern public health surveillance was organised. Effective surveillance, including notification, remains an integral part of the response. When cholera is suspected in an area that was free from cholera, then International Health Regulations require that the diagnosis should be laboratory confirmed as soon as possible and the World Health Organization immediately notified. Cholera is one of only three diseases, including plague and yellow fever, where this action is required. All cases of watery diarrhoeal illness associated with severe dehydration, particularly in people more than five years of age should be responded to as cholera until proven otherwise.

In addition to careful investigation of water supplies, particular attention should be paid to other common sources, which include street vendor

sanitation and funerals. Funerals of cholera victims have served as highly effective sites for disease transmission in communities where tradition dictates that family members responsible for preparing the corpse for burial should also prepare the feast for guests. Training programs and careful monitoring of street vendors, disinfection of corpses and restriction of funeral feasts have aborted outbreaks where these transmission routes have been implicated.[27]

The value of "Moore" pads for environmental monitoring is limited and the attendant cost does not justify widespread environmental deployment. Their use should be restricted to targeted epidemiological investigations following detection of a cholera case and for confirming the termination of environmental bacterial circulation at the end of an epidemic. Deployment of "Moore" pads in mines or residential areas with centralised sewage collection may provide early warning of cholera presence.

It should be emphasised that staff training in clinical management, securing of emergency supplies, and rapid response to the cholera syndrome of profuse watery diarrhoea have proved successful in containing cholera in developing settings.[28]

What is the risk of cholera for the traveller?

The risk of cholera is minimal for the average business or holiday traveller.[29] Typically travel-associated cases occur among people who have visited friends or relatives in their countries of origin in the developing world.[30]

As travel restrictions, trade embargoes and vaccination have proven ineffective for controlling cholera, travel to cholera endemic areas is generally not restricted.[31] In addition travellers can take simple precautions to minimise their risk. These include drinking only water that has been boiled, or treated with chlorine or iodine, tea or coffee made from boiled water, and carbonated bottled beverages. Ice should be avoided, as the source water usually cannot be guaranteed in developing countries.

In addition travellers should be cautioned that food and beverages should not be bought from street vendors. Foods should be thoroughly cooked and eaten while still hot. Fruits should only be consumed if personally peeled. Undercooked or raw fish and shellfish are hazardous, particularly as the latter accumulate Vibrios through filter feeding in contaminated water, and should thus be avoided. All vegetables should be cooked and salads avoided.

It is important to advise the prospective traveller to ascertain the source and monitoring of water and food at their destination prior to departure. A good rule of thumb is the World Health Organization's simple guideline: "Boil it, cook it, peel it, or forget it".

To vaccinate or not to vaccinate against cholera?

Cholera vaccination remains a controversial issue. Despite the 26th World Health Assembly abolishing the right of countries to impose a requirement for a cholera vaccination certificate in 1973, this has not prevented countries like Egypt and Uganda demanding proof of vaccination from KwaZulu-Natal travellers during the current epidemic. Various commercial interests are also guilty of providing inaccurate advice on the value of cholera vaccination.

Three vaccines are commercially available. The original killed vaccine has largely been replaced, because of its unacceptable adverse events profile, by a whole-cell killed vaccine that includes a B-sub-unit (WC-BS) and a live attenuated vaccine, CVD 103-HgR. However these latter vaccines only provide approximately 62% protective efficacy against El Tor V. cholerae.[32,33] The reasonable protection against disease offered to healthy military recruits is of short duration, i.e. a few months, and does not provide protection against other cholera serotypes.

Potential disadvantages accompany cholera vaccination. As vaccinated individuals still become infected and excrete organisms, vaccination is unable to affect the spread of cholera. It may also generate a false sense of security with resulting relaxation of more important methods for control. Recently the role of cholera vaccination in refugee camps has been reconsidered but even in this setting vaccination against El Tor cholera appears to have borderline cost-effectiveness.[34,35]

Conclusion

Epidemic cholera is an indicator of severe under-development.[36] Historical proof of cholera contamination of municipal water supplies provided the impetus for the sanitary revolution. Cholera should still continue to catalyse infrastructural development, particularly to improve water and food safety.

During epidemics, the focus of control must remain public health preparedness and sustained community awareness.[37] Prompt assessment and aggressive corrective fluid management by family practitioners will ensure excellent treatment outcomes.

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Key Messages

- **Cholera is a severe diarrhoeal illness which can lead rapidly to dehydration and death**
- **Of 193 recognised "O" serogroups of V. cholerae only 01 and 0139 cause epidemics**
- **The key to cholera management is appropriate and aggressive fluid replacement**
- **The role of antibiotics in the management of cholera remains adjunctive**
- **Only the quinolones are effective against local cholera strains and should only be used in the critically ill adult patient (oral ciprofloxacin 1 gm stat)**
- **All cases of watery diarrhoeal illness associated with severe dehydration, particularly in people above five years of age, should be responded to as cholera until proven otherwise**