EDITORIAL

CHOLERA — THE NEW EPIDEMIC?

The article by Athan *et al.*[1] in this issue of the *SAMJ* is an admirable example of what can be achieved if a health department is adequately prepared for an outbreak of any infectious disease. Timely staff training, education of the local population and vigilance on the part of local health authorities undoubtedly contributed to the containment of an outbreak of cholera due to *Vibrio cholerae* O1 El Tor Ogawa that could otherwise have reached epidemic proportions. Unfortunately it is too soon to celebrate, and there can be no room for complacency. The Mozambican cholera epidemic is ongoing, and although the situation may have quietened with the onset of winter, as summer approaches and the rivers start to flow again we can expect the epidemic to resurge in Mozambique and possibly reappear in the South African population at risk. Vigilance and pro-active measures will be required once more to contain the South African cases and limit them to Mpumalanga, with the occasional case imported to Gauteng or elsewhere.

During the last outbreak of cholera in this country in the early 1980s, 25 251 laboratory-confirmed cases were reported between 1980 and 1986. This epidemic was caused by *V. cholerae* O1 El Tor Inaba,[2] and took 7 years finally to disappear. There were 348 deaths.[2] An 'acceptable case fatality rate' of less than 1% can be achieved by improved treatment, particularly oral rehydration therapy.[3]

Rehydration therapy is the single most critical treatment modality in cholera. Cholera toxin is an AB_5 heterohexamer. The B subunits bind to the GM_1 ganglioside on the brush border of the small-intestine epithelium. The A subunit then causes ADP-ribosylation of adenylate cyclase, resulting in elevated cAMP and active efflux of electrolytes, the osmotic pressure causing large quantities of water, sometimes litres a day, to be lost through the gastro-intestinal tract.[4]

It is now recognised that in approximately 90% of cases cholera is mild and may be indistinguishable from other acute diarrhoeal diseases.[3] In this group of patients oral rehydration should be adequate. In patients with severe diarrhoea, particularly those in hypovolaemic shock, intravenous rehydration with Ringer's lactate is required.[3] These patients should be placed on oral rehydration solution as soon as they can drink, eveh if further intravenous rehydration is necessary.

The use of antibiotics in the treatment of cholera is controversial. Although it has been shown that they shorten the course of the disease,[5,6] once dehydration is corrected the patient normally recovers fully, even when not given antibiotics. The World Health Organisation recommends optional oral antibiotics including doxycycline for adults or furazolidone (not available in South Africa), trimethoprim-sulfamethoxazole, or erythromycin for children, or as alternatives to doxycycline in adults.[3] The strain currently involved in cases in South Africa is resistant to all of these in the laboratory, although resistance to erythromycin does not necessarily reflect the *in vivo* situation. Antimicrobial resistance of *V. cholerae* to multiple antibiotics is a worldwide trend.[7-11] Multiple antibiotic resistance in *V. cholerae* O1 has been shown to be mediated by a plasmid[9-11] which is easily transferable between *V. cholerae* and other Gram-negative strains.[11] This implies that under selective antibiotic pressure, even in the absence of a cholera epidemic, a reservoir of antibiotic resistance genes ready for transfer to *V. cholerae* can be maintained among indigenous intestinal bacteria.

Antibiotic resistance is thought to have originated from extensive use of tetracycline prophylaxis and treatment in cholera epidemics.[7-9] As plasmids frequently encode resistance to more than one antibiotic, the use of a single antibiotic may select for resistance to others.[9,10] Large-scale antibiotic prophylaxis and treatment in cholera is therefore strongly discouraged for a number of reasons: (*i*) it may select for plasmid-mediated antibiotic resistance; (*ii*) most cases are not severe and can be controlled with oral rehydration therapy; and (*iii*) large-scale antibiotic prophylaxis, like large-scale vaccination, has never been shown to be effective in preventing a cholera outbreak.[3]

Recently *in vitro* and *in vivo* studies have shown that fluoroquinolones are effective in the treatment of cholera.[12,13] Moreover, single-dose therapy with a fluoroquinolone cleared *V. cholerae* O1 and *V. cholerae* O139 from the stool more rapidly than single-dose doxycycline.[13] Although quinolone resistance is primarily chromosomal, and therefore should not be affected by plasmid-mediated resistance to other antibiotics, a recent report described plasmid-mediated quinolone resistance, associated with resistance to multiple antibiotics as well as antiseptics.[14] The introduction of fluoroquinolones for the treatment of cholera should therefore be viewed with caution even though they appear (apart from cost considerations) to be the logical choice for treatment of cholera caused by the drug-resistant strain prevalent in southern Africa.

There are a number of reasons why we should expect cholera to re-emerge this summer. Although the departments of health in Mpumalanga and Gauteng, the two provinces affected by the most recent outbreak, have shown themselves admirably prepared for the disease, conditions supporting the continuation of the epidemic remain unchanged. Large areas of Mpumalanga still have an inadequate piped water supply and poor sewage disposal, and the local population must rely on faecally polluted rivers for water. Migrant labour from Mozambique has become a fact of life in South Africa, as this country is viewed as a source of wealth for its poorer neighbours. These migrant workers pass through Mpumalanga as they head towards Gauteng, or try to find work on the farms

in Mpumalanga and settle there. Cholera, moreover, is largely a disease of poverty, and the current economic crisis in the country will inevitably result in more people living under conditions of poor hygiene, which expose them to this scourge.

V. cholerae is well adapted to living in chemically polluted water, and our rivers are notoriously polluted.[15] Furthermore, iron contamination of water through rusty pipes and other iron-containing structures promotes the survival and multiplication of the organism and stimulates toxin production.[15-17] Storage of drinking water in iron containers has been shown to be a potential risk factor for the transmission of cholera.[16]

So what can we do? Those of us in the private sector and the State health departments should maintain vigilance and have a high index of suspicion in situations where we know the patient is at risk for contracting the disease. Ongoing education of health professionals in areas at risk is mandatory, and the provincial health departments need to remain prepared. Creating awareness in 'at risk' populations and teaching them basic hygiene and infection control will assist in limiting an outbreak. The Department of Health has prepared a document on the management of a cholera outbreak or epidemic, and these guidelines should be followed to protect the population as a whole. In suspected cases, especially in adults and not necessarily only those with severe diarrhoea, stools should be sent for culture of *V. cholerae* O1. Close liaison between laboratories and health authorities should be established, and *V. cholerae* isolation should immediately be reported to the local health authority, which in turn should introduce urgent containment procedures based on focused investigative information relating to the rapid identification of new cases, the likely water source and modes of transmission. Finally, we need to realise that we are not living in isolation, and as human traffic increases across our borders and within them, we will continue to be exposed to emerging and re-emerging infectious diseases, including those we believed would never affect us again. It is critical that all members of the health community co-operate in combating disease and that they assist the population to do the same.

K H Keddy
H J Koornhof

South African Institute for Medical Research
Johannesburg

1. Athan E, Donohue S, Durrheim D. A cholera outbreak in a rural region of South Africa. *S Afr Med J* 1998; **88:** 1306-1308 (this issue).
2. Küstner HGV, Du Plessis G. The cholera epidemic in South Africa, 1980 - 1987. *S Afr Med J* 1991; **79:** 539-544
3. WHO Global Task Force on Cholera Control. *Guidelines for Cholera Control* (WHO/CDD/SER/80.4). Geneva: WHO, 1992.
4. Spangler BD. Structure and function of cholera toxin and the related *Eschericia coli* heat labile enterotoxin. *Microbiol Rev* 1992; **56:** 622-647.
5. Burans JP, Podgore J, Mansour MM, *et al.* Comparative trial of erythromycin and sulphatrimethoprim in the treatment of tetracycline-resistant *Vibrio cholerae* O1. *Trans R Soc Trop Med Hyg* 1989; **83:** 836-838.
6. Khan WA, Begum M, Salam MA, Bardhan PK, Islam MR, Mahalanabis D. Comparative trial of five antimicrobial compounds in the treatment of cholera in adults. *Trans R Soc Trop Med Hyg* 1995; **89:** 103-106.
7. Mhalu FS, Mmari PW, Ijumba J. Rapid emergence of El Tor *Vibrio cholerae* resistant to antimicrobial agents during the first six months of fourth cholera epidemic in Tanzania. *Lancet* 1979; **1:** 345-347.
8. Glass RI, Huq I, Alim ARMA, Yunus M. Emergence of multiply-antibiotic resistant *Vibrio cholerae* in Bangladesh. *J Infect Dis* 1980; **142:** 939-942.
9. Finch MJ, Morris JG, Kaviti J, Kagwanja W, Levine MM. Epidemiology of antimicrobial resistant cholera in Kenya and east Africa. *Am J Trop Med Hyg* 1988; **39:** 484-490.
10. Tabtieng R, Wattanasri S, Echeverria P, *et al.* An epidemic of *Vibrio cholerae* El Tor Inaba resistant to several antibiotics with a conjugative group C plasmid coding for type II dihydrofolate reductase in Thailand. *Am J Trop Med Hyg* 1989; **41:** 680-686.
11. Glass RI, Huq MI, Lee JV, *et al.* Plasmid-borne multiple drug resistance in *Vibrio cholerae* serogroup Ol biotype El Tor: Evidence for a point source outbreak in Bangladesh. *J Infect Dis* 1983; **147:** 204-209.
12. Morris JG, Tenney JH, Drusano GL. *In vitro* susceptibility of pathogenic *Vibrio* species to norfloxacin and six other antimicrobial agents. *Antimicrob Agents Chemother* 1985; **28:** 442-445.
13. Khan WA, Bennish ML, Seas C, *et al.* Randomised controlled comparison of single-dose ciprofloxacin and doxycycline for cholera caused by *Vibrio cholerae* Ol or O139. *Lancet* 1996; **348:** 296-300.
14. Martínez-Martínez L, Pascual A, Jacoby GA. Quinolone resistance from a transferable plasmid. *Lancet* 1998; **351:** 797-799.
15. Patel M. The effect of some physico-chemical parameters on the survival and toxigenicity of *Vibrio cholerae*. PhD thesis, University of the Witwatersrand, Johannesburg, 1996.
16. Patel M, Isaäcson M, Gouws E. Effect of iron and pH on the survival of *Vibrio cholerae* in water. *Trans R Soc Trop Med Hyg* 1995; **89:** 175-177.
17. Patel M, Isaäcson M. The effect of iron on the toxigenicity of *Vibrio cholerae*. *Am J Trop Med Hyg* 1998 (in press).

IF, WHEN AND HOW TO TREAT GASTRO-OESOPHAGEAL REFLUX — THE NEONATOLOGIST'S DILEMMA

In the introduction to their comprehensive review,[1] Rode *et al.* reference several statements, *inter alia* (*i*) despite the oesophagus being structurally and functionally intact from an early age (33 weeks' gestation), synchronous peristaltic activity is present in less than 60% of newborns, and approximately 40% of the peristaltic waves are incomplete or retrograde; (*ii*) particularly controversial is the role of the medical treatment of persistent occult gastro-oesophageal reflux; (*iii*) persistence with ineffective long-term medical therapy may unnecessarily place the infant at risk; and (*iv*) the prevalence of pathological reflux among low-birth-weight infants is 3 - 10%, with symptoms of irritability, apnoea, bradycardia, vomiting and deterioration of bronchopulmonary disease.

From this the reader could easily formulate an opinion along the following lines: neonates (and, more likely, premature neonates) are predisposed to reflux; there might be adverse consequences of not intervening surgically in the neonate or infant in whom motility does not normalise; and it is relatively easy to identify candidates for such intervention on the basis of symptomatology. However, neonatologists and paediatricians dealing with premature and full-term infants would have a very different reaction to these statements, recognising that they are perhaps opening the door to unnecessarily aggressive treatment, both medical and surgical.

Recent reviews on the subject indicate that virtually all infants have some degree of reflux in the newborn period, while approximately 50% of healthy infants still have