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EDITORIAL

Prospects for Control of Cholera with Oral Vaccines

The control of cholera seems to remain outside the reach of today's world. An ancient disease, whose "home" has been the Ganges delta since early recorded history, it has encompassed the globe on several occasions in the past 200 years, as modes of transportation have gradually made our world smaller. In 1991, the 7th pandemic, which began in Indonesia in 1958, completed its spread to South America. This present pandemic, with literally millions of cases and hundreds of thousands of deaths, has spread relentlessly in spite of the fact that 1) cholera is perhaps the best understood of all the infectious diseases in terms of pathogenesis and pathophysiology, 2) treatment of cholera is available that will essentially prevent all deaths, if it is applied appropriately, and 3) prevention of the disease can be obtained with relatively minimal hygienic precautions.

Several reasons can be given to explain this phenomenon:

1. The cholera vibrio (*Vibrio cholerae* 01), although not a particularly hardy organism by bacterial measures, is unusually well adapted to survive in aquatic environments, particularly those with low salinity, such as brackish waters that occur in estuaries, and in association with shellfish. Recently algae and plankton have also been postulated as possible reservoirs for these organisms. Therefore, human hosts are not critical for the survival or transmission of the organisms in nature; humans are necessary, however, for the transmission of the disease widely as is seen in epidemics and in the present pandemic. Such transmission can only occur in places where sanitation is poor, and drinking water is heavily contaminated with faeces, thus allowing the widespread distribution of vibrios from the faeces of one person to the mouths of others. Unfortunately, much of the world's population lives in circumstances where such inadequate water and sanitation prevail.
2. Although *V. cholerae* is only one of many microbial agents that produce diarrhoeal diseases, the disease it produces is unique among them. Untreated, it has a very high mortality rate of greater than 50%, the average time from onset of symptoms to the occurrence of life threatening dehydration is approximately 12 hours, and some intravenous fluids are usually necessary to treat the disease; oral rehydration alone will not adequately prevent death. In areas where cholera is occurring in epidemic form, particularly for the first time, young adults, especially males, are the ones who most frequently develop fatal disease. Cholera is the only enteropathogen to cause major epidemics and pandemics; the only other diarrhoeal pathogen that may show a somewhat similar pattern is *Shigella dysenteriae* type 1 (the Shiga bacillus).
3. The immunological protection afforded by the natural disease, though substantial for the first several years, is clearly not lifelong, and susceptible persons always seem to be available, even in areas of high endemicity, such as Bangladesh. Parenteral vaccines, available for the past 100 years and initially thought to provide substantial protection, have been shown to provide only limited protection for a short period of time and have been abandoned as a possible public health measure to control the disease.

What then are the possibilities for averting the tremendous morbidity and mortality due to this global disease?

1. We can improve the water and sanitation in those areas of the world where they are known to be less than ideal. This is clearly already being done as development proceeds in all the countries of the world. But it is a long term solution, and one that will take many decades and much capital to achieve. In the meantime, efforts at controlling the transmission of the organisms in the environment at the personal or micro level are underway; these are being done through educational and social efforts to improve the use of safe water and latrines and handwashing. Again, these changes will only come slowly, as the educational and literacy levels of the world's population improve.
2. We can improve the therapy of the disease, which is well understood pathophysiologically. We know now that anyone with cholera can be cured, as long as he/she has a heartbeat at the time treatment is begun; death should be a rarity. Obviously this cannot be improved upon. What can be improved is making the treatment more available to those with the disease. This will require that adequate supplies are available (appropriate intravenous fluids such as Ringer's lacate and/or normal saline; adequate amounts of oral rehydration fluids; and adequate amounts of antibiotics, such as tetracycline) and that there are adequate trained personnel to administer the treatment appropriately. Most of the developing countries now have Diarrhoeal Diseases Control Programmes (CDD's), but these are often understaffed and poorly funded and generally not adequate to manage large numbers of cholera

patients. Furthermore, they are often not located in the areas where cholera may be occurring, and are therefore not easily accessed in emergency situations. The purpose of CDD's is primarily to treat the much larger numbers of diarrhoeal diseases that occur in young children, most of which are not cholera, and for this purpose these programmes work very well. ORS is the mainstay of therapy, the diseases treated are usually much less acute, and travel to nearby centers for adequate treatment is possible. The improvement of the national CDD programmes is certainly to be encouraged, but their limitations in terms of cholera management should be realised.

3. We can develop an effective, low-cost vaccine that can prevent large segments of the population from developing the disease and thus requiring treatment. Such a vaccine, as we now know from many animal and volunteer experiments using a wide variety of enteric pathogens, should be an oral vaccine which stimulates maximally the secretory Ig A antibodies of the small intestine. Ideally, it should produce no side effects, should be effective following a single dose, and should produce long lasting protection, preferably for several years. Unfortunately this "ideal" vaccine does not yet exist, but considerable efforts are being made to develop such a product that can be used as a public health tool.

At present there are two cholera vaccine candidates that show promise for wide-spread use: a non-living vaccine, which consists of killed vibrios and the B subunit of the cholera enterotoxin (WC/B), and a live vaccine, which consists of an attenuated strain of *V. cholerae* 01, which also produces the B subunit of the cholera enterotoxin (CVD 103-HgR).

WC/B VACCINE. The WC/B vaccine, which consists of 1×10^{11} mixtures of killed classical and El tor biotypes of the two serotypes of *V. cholerae* 01 (Inaba and Ogawa) and 1 mg of purified B subunit, has been field tested in Bangladesh over a 5-year period in children, ages 2 - 15 years, and women of child-bearing age (1,2). Given in 3 doses, 6 weeks apart, along with an antacid (to protect the B subunit which is acid labile), it produced no side effects. Its protective efficacy lasted for 3 years and the overall rate of protection was 50%. Cumulative protection was much higher in children above 5 years of age and adults (63%) than in children between the ages of 2 and 5 years, in whom it was only 26%. Protection was considerably higher (85%) in all age groups during the first 6 months following administration. Although the trial was not designed to test the efficacy of two vs three doses of vaccine, analysis of the data from persons who did not receive the entire vaccine series indicated that two doses were as effective as three; one dose was not protective. During the first year of the trial, there was also a 48% reduction in admissions to the treatment centers for severe dehydrating diarrhoea, and there was a 45% reduction in mortality in adult women due to severe diarrhoea (3). It was determined that protection was less against cholera due to El tor vibrios than that due to classical vibrios, and was also less in persons with group O blood type. There was no protection against diarrhoeas due to non-cholera vibrios, but there was a substantial protection (67%) against diarrhoea caused by *Escherichia coli* which produced heat-labile enterotoxin (LT), in the first 3 months following vaccination(4). This was presumably because of the immunological similarity between the B subunits of the cholera and *E. coli* enterotoxins.

Another non-living vaccine, which consisted of the whole cells of *V. cholerae*, but without the B subunit (WC), was tested at the same time as WC/B. WC gave similar results to WC/B, but did not provide the high degree of protection during the first few months after vaccination, and did not protect against LT-producing *E. coli*. Because of these deficiencies, further consideration of this vaccine will not be given.

The major limitations of WC/B are: the degree of protection, which is less than optimal, particularly in small children, the need for two doses of vaccine, rather than one, and the need to be given with antacid. The major advantages are: the lack of side effects, the low cost (potential), and delivery of the vaccine will probably not require a strict cold chain.

CVD 103-HgR VACCINE. This vaccine consists of 109-11 colony-forming units of strain CVD 103-HgR, which is a derivative of *V. cholerae* 01 strain Inaba 569B, which has been attenuated genetically so that it makes only the B subunit of the enterotoxin and has an identification marker for mercury resistance (5). It is also given with antacid to protect the acid-sensitive vibrios in their journey through the stomach. A single dose has been shown to induce substantional levels of antibodies in volunteers, and to provide protection against challenge with virulent organisms without producing side effects. (Earlier versions of this vaccine had been unacceptable because they produced diarrhoeal symptoms in a small, but significant, percentage of volunteers (1). This vaccine is being tested for immunogenicity in adults and children living in developing countries (Thailand and Indonesia) but has not been tested for efficacy in a field trial.

The major advantages of this vaccine are: only a single dose is required, and no side effects are produced. The major disadvantages are: a cold chain is necessary to ensure viability, and the need to be given with antacid.

The cost of production and distribution of CVD 103-Hg may be higher than WC/B, although accurate cost estimates have not yet been established. Unfortunately, no data are available to compare the protective efficacy of the CVD 103-Hg with WC/B under field conditions.

Should the use of oral cholera vaccines be included as a public health measure to control cholera, either in endemic or newly invaded areas of the world?

Clearly the answers are not known at the present time, and data necessary to provide the answers are still needed. In South America, an area which has not had cholera for the last 100 years, the WC/B vaccine is being readied for field testing. In Bangladesh, where cholera is, and has been, endemic for hundreds of years, there is a definite need for an effective vaccine. In 1991, there were an estimated 300,000 cases of cholera in Bangladesh, with approximately 10,000 deaths (6). Most of the fatal victims of the disease had no access to treatment, and were not seen by anyone qualified to treat the disease. Since Bangladesh, like all developing countries, has limited resources to invest in cholera control, any public health measures will need to be cost effective. Clearly the CDD programme needs to be strengthened, so that cholera victims could receive adequate treatment. But another control measure, that of vaccination, should also be further investigated, using the oral cholera vaccine that is presently available (WC/B). In order to be used in Bangladesh, the cost of the vaccine will need to be low (estimated at approximately 5 – 10 U.S. cents per dose)(6); the only way that the vaccine could be produced inexpensively would be to have it made locally in Bangladesh. The vaccine will need to be given in two doses, with antacid, and it can be timed to be given on a mass scale immediately before the epidemic cholera seasons in Bangladesh, which are known to occur in April – May and again in September – November. In Bangladesh 90% of cholera cases occur in persons above the age of 2 years (50% occurs in persons above the age of 5 years) (7); the target population (with the available data) would thus be all persons over the age of 2 years. All persons vaccinated would thus experience a high degree of protection against cholera for the first 6 months following vaccination (including protection against LT – producing *E. coli*); the children under the age of 5 years would of course need booster doses within 6 – 12 months. Children over the age of 5 years and adults would be expected to receive approximately 60% protection for 3 years and would require booster doses at that time.

In order to determine the feasibility of such an approach, data need to be gathered on the possibilities of local vaccine production in Bangladesh and its wide – spread distribution.

Admittedly, the WC/B vaccine is the first generation of oral cholera vaccines. Although it has limitations, it would seem that the degree of protection that it can provide would be useful in situations where treatment of the disease is less than optimal, particularly if the cost of delivering the vaccine were low.

If the CVD 103 – HgR vaccine (the second generation vaccine) proves also to provide similar or perpaps even higher degrees of protection, (either greater efficacy or longer duration) it should also be considered for use in a similar way. In the meantime, improvements are being made in the non – living vaccine by the addition of newly – recognised virulence (colonization) antigens (the toxin co – regulated pilus antigen (TCP), and the cell – bound hemagglutenin of El tor (MSHA) which are not present in the present WC/B vaccine. Should these prove to stimulate additional protective antibodies, they can be included in the formulation of the non – living vaccine.

Since there are few areas in the world where cholera is endemic, relatively predictable, accessible, and of great public health importance, Bangladesh would seem to be the ideal place to evaluate the usefulness of an oral cholera vaccine as a public health control measure, both in production and implementation.

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R Bradley Sack

Associate Director
International Centre for Diarrhoeal Disease Research, Bangladesh, GPO Box 128, Dhaka 1000, Bangladesh