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EDITORIAL

When Should Cholera Vaccine be Used in Cholera-endemic Areas?

The paper by Vu Dinh Thiem *et al*. in this issue of the Journal provides valuable documentation of the costs for providing killed oral cholera vaccine during a mass-vaccination programme in Vietnam (1). Vietnam is the only country where cholera vaccine is now being given to endemic populations, although many other countries in Asia and Africa have regular seasonal outbreaks of cholera. This raises the question of defining the circumstances for using cholera vaccine in endemic areas.

The World Health Organization (WHO) has recommended use of killed oral cholera vaccine in refugee populations of Africa (2), but it has not yet formulated a policy for use of either the live or killed oral vaccines in areas endemic for cholera (Chaignat C-L. Personal communication, 2003). There are several reasons why it has been difficult for WHO to formulate such a policy. The true burden of disease from cholera is not well-understood since many nations with cholera do not report it because of fears of restriction on trade and travel, and when they do, the numbers likely do not reflect the true rates of infection. Outbreaks or epidemics are more likely to be reported than cases occurring in endemic situations, and many endemic areas do not have the laboratory or epidemiological surveillance resources to document accurate rates. Since countries are not reporting cholera, it becomes difficult for WHO to recommend a vaccine for an infection that is not recognized to occur (3).

However, many geographic areas continue to have a large burden of disease from cholera, often exceeding one hospital case per thousand annually. In these areas, cholera is well-known to the local population, they greatly fear it and would likely welcome a vaccine providing protection.

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Since the recommendations differ between refugee situations and endemic areas, it would be useful to review some differences in these two situations (Table).

Table. Comparison of cholera in endemic and refugee situation in relation to cholera vaccine use

Endemic situation
Partially immune
Possible to have surveillance over period of time
Would need to use routine services
More emphasis on cost-effectiveness evaluation for the long term
Less public awareness
'National' problem, so little chance for international funds
Refugee situation
No background surveillance
New healthcare system with 'outsiders' providing assistance
Higher public awareness internationally
More funds for 'humanitarian emergencies' from international donors

In endemic areas, people have some degree of acquired immunity, and this pre-existing immunity modulates the effectiveness of any vaccine. It is also possible to establish surveillance for cholera and, thus, to determine a true burden of disease. When patients develop symptoms of cholera, they use the routine primary healthcare facilities available for any other diarrhoeal disease, including government hospitals or traditional providers. In either case, the decision for implementing a cholera vaccine programme would logically depend on an analysis of its cost-effectiveness from a national perspective. Because the patients are using routine facilities, there is likely to be less public awareness of the problem, and it would be handled as a national problem, with little opportunity for urgent international funding. Thus, the funds to deal with the problem will need to come from a regular budgetary provision.

By contrast, the situation of cholera outbreaks in refugees is quite different. Refugees often have little or no immunity since they may have migrated into a cholera area from one that was not cholera-endemic. By definition, there has been no background information on expected disease incidence since there has been no surveillance. Based on other similar situations, however, rates might be expected to be high (4). In contrast to the endemic area, medical care is often provided by special facilities for refugees, and these facilities are often provided by international agencies. These agencies are often well-connected to journalists who may publicize the cholera epidemics, and this publicity may generate substantial emergency funds from international donors. Cost-effectiveness considerations may then take a secondary role to the emergency humanitarian need from the epidemic.

The experience of ICDDR,B in Bangladesh might be cited to illustrate the situation in a cholera-endemic area. In its rural Matlab field area with a population of over 200,000, the annual incidence has generally been from 1 to 5 case(s) of cholera per 1,000 as detected by hospital surveillance (5-7). Based on past epidemiological studies, it is known that there is likely to be more than 4 milder cases occurring in the community for every case coming to hospital (8), suggesting a likely true incidence of cholera in the range of 4 to 20 cases per 1,000. Many of the cases occur during cholera seasons before and after the monsoons, and these have been predictable (7). Other parts of the country also have predictable seasons, although their rates of illness may differ from that in Matlab (7). At the ICDDR,B hospital in urban Dhaka, an average of 20,000 cholera patients are treated annually, and these numbers have exceeded 50,000 cases during peak years (Annual Reports, ICDDR,B). Thus, it can be concluded that cholera constitutes a substantial disease burden in Bangladesh, and a vaccine should at least be considered as a public-health tool.

There have been constraints, however, to the use of cholera vaccines, and many of these are reflected in some 'old notions' about the characteristics of a suitable vaccine. Some examples of these old notions include the following:

- *Vaccine protection should be life-long*: In fact, life-long protection may not be needed if booster doses are cheap and easy to provide. Certainly, distribution of oral vitamin A is a very effective public-health intervention, although it is given every 4 to 6 months because it has been relatively inexpensive to purchase and is safe and easy to administer.

- *A vaccine should be given in a single dose*: Again, a single dose is not needed if the vaccine is sufficiently cheap and easy to provide and is acceptable to the population.

- *A vaccine should have a very high protective efficacy*: Although a vaccine must be efficacious, the public-health benefit is not measured by high protective efficacy, but rather by a measure of the numbers of cases or deaths averted, or disease-related costs averted. A vaccine for a very common or very expensive disease with a modest protective efficacy may provide more public-health benefit than a highly efficacious vaccine against a less common or inexpensive disease.

- *Improved water and sanitation should be the strategy for cholera*: Clearly, cholera could be controlled if all people drank clean water and used modern sanitation. Unfortunately, these are not possible in the near future in cholera-endemic areas. Withholding vaccine to support a water/sanitation strategy would be neither prudent nor ethical if the vaccine would potentially save populations from contracting the illness. In fact, a water/sanitation intervention would likely benefit from vaccines, since an immunized population would excrete fewer organisms into the environment, resulting in less pollution of the surface waters. Similarly, persons with improved water and sanitation would be exposed to a lower inoculum, making the vaccine more effective. Thus, the two interventions are likely to protect in a synergistic manner.

- *An 'ideal' vaccine should be as follows*: Various documents have outlined an ideal vaccine for cholera, as they have for other infections. Although the *ideal* vaccine would be an excellent contribution, "ideal may be the enemy of the good." An ideal vaccine may not be developed in the near future, but others that are not ideal may still provide substantial benefits.

- *A vaccine is no longer needed since treatment is so successful*: Treatment is very effective with a case-fatality rate of less than 0.5% among those who receive good treatment. Patients should not die of cholera in this era of good case management; however, many patients do not receive good case management because they do not have access to this care. Lack of access may be due to being geographically remote, economically poor, or may be due to other sociocultural reasons. Many of these cholera patients who do not have access to treatment could receive vaccine; thus, denial of a useful vaccine for these persons raises questions of equity. It is known that vaccines are among the most equitable health services, while treatment facilities are often not equitable even though they may be targeted to the poor. Also, from a more practical standpoint, cholera is an acute disease in which treatment is urgently needed within a few hours, while vaccines may be delivered in a more orderly and convenient manner.

Currently, two oral vaccines are licensed in different countries. To be licensed by the drug authorities in industrialized countries, the vaccines must be shown to be safe and effective. To be accepted as public-health tools in developing countries, however, they must have many additional attributes. For example, the vaccine should address a major public-health problem, it must be inexpensive, convenient to store, distribute, and administer, its use must be readily learnt, it must be acceptable to the local population, economically sustainable, and there must be a strong commitment from national governments. In the case of the currently-licensed live and killed oral cholera vaccines, these have been shown to be safe and effective, but the other requirements for public-health use have not been demonstrated, and further work is needed to establish their usefulness in endemic areas.

Recently, we developed a computer model to explore the cost-effectiveness of oral cholera vaccines in an attempt to identify the most important determinants which might indicate that a vaccine would be cost-effective. The model uses the example of Bangladesh and assumes that the routine health system would be able to provide emergency care for cholera patients at its district or sub-district health facilities. It assumes that all deaths would be averted with proper rehydration management, but if this was not available, the case-fatality rate would be 20% (The true untreated case-fatality rate is likely be higher). The model assumes as benefits only the deaths that would be prevented and did not consider other benefits from treating patients that would have survived without treatment. Thus, the model likely underestimates the true medical benefits to non-fatal cases since some untreated patients are likely to suffer from complications. It also underestimates the benefits since there continue to be deaths in cholera patients and some of these deaths could be prevented with the vaccine.

The model uses costs that are reasonable estimates for Bangladesh but the model did not undertake a true costing study to determine the actual costs in an actual costing study. The estimated costs included costs of treatment, lost wages, and costs of transport to the hospital. Other variables in the model include the expected age-specific incidence of cholera, the age-specific protective efficacy of the vaccine, and the duration of protection. It assumes a three-year protective efficacy of 75% for adults and older children and 25% for children aged less than five years. It does not include the costs of training of the staff in cholera treatment, but it does estimate a daily rate for hospital charges of $15 per day as well as additional charges for administering intravenous fluids as needed. Obviously, these costs would be different in different countries. In the model, the cost per death averted with treatment was $350, so this is used as a benchmark aginst which to measure cost-savings.

Being a cost-effectiveness model rather than a cost-benefit model, it expresses the outcome in terms of costs per death averted or cost per hospitalization averted. Thus, it does not include the economic benefits to the family or the economy of averting the cholera deaths.

Based on sensitivity analyses, it was clear that the cost of the vaccine and the expected incidence of the disease were the most important determinants in making the vaccine either cost-effective or ineffective. This is illustrated in the Figures 1-3.

Fig. 1. Calculated cost-effectiveness of a cholera vaccine costing US$ 0.40 depending on the expected rate of cholera. Outcome is expressed as cost per death averted or cost per hospitalization averted

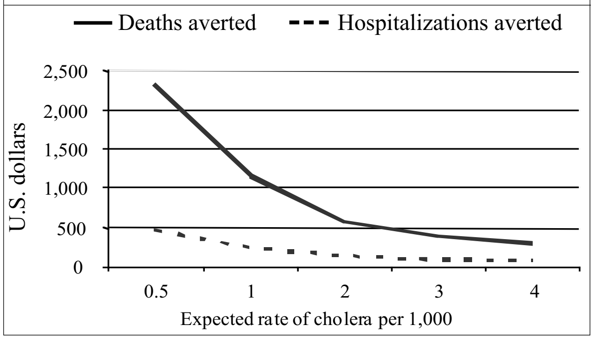


Figure 1 shows the calculated cost per death averted and cost per hospitalization averted with a cholera vaccine costing US$ 0.40 when used in populations with a variable expected rate of cholera. With a low expected incidence (0.5 per 1,000), the costs per death averted exceed US$ 1,000 but as the expected cholera rate increases to 3 per 1,000, these costs per death averted drop substantially, and in situations with very high rates, the use of the vaccine is cost-saving. The curves for cost per hospitalization averted show a similar relationship to expected rates.

Figure 2 shows the calculated cost-effectiveness depending on the cost of the vaccine when the hypothetical vaccine programme is implemented in a population with an expected rate of 3 per 1,000, typical of the Matlab field area. The cost per death and hospitalization quickly rises when the cost of the vaccinations exceeds US$ 1.00.

Fig. 2. Calculated cost-effectiveness of a cholera vaccine depending on the cost of the vaccine, varying from US$ 0.40 to US$ 6.40 per immunized person assuming the programme is implemented in a population with an expected rate of 3 per 1,000

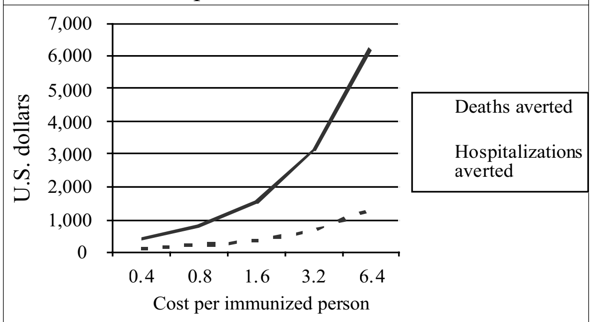
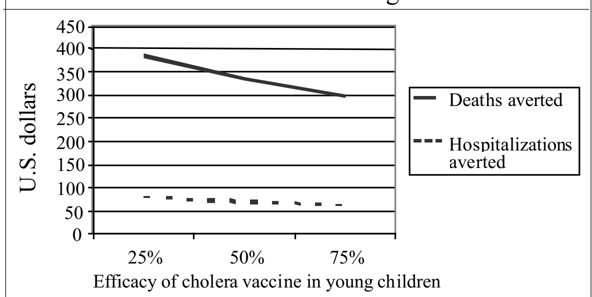


Figure 3 shows the calculated cost-effectiveness with a hypothetical 'improved' vaccine. This analysis was carried out since some have suggested that a deficiency of the killed oral cholera vaccine was the relatively short duration of protection in young children relative to older children and adults yielding a lower three-year efficacy in young children (9). Thus, this model was used for testing the benefit of improving the vaccine to provide longer-lasting protection in young children so that protection of young children and adults would be similar (75%). As shown in Figure 3, the cost-effectiveness of this hypothetical, improved vaccine was better, but the shallow slope of the cost-effectiveness curve suggests that the improvement yielded only modest benefits in terms of cost-effectiveness.

Fig. 3. Cost-effectiveness of cholera vaccine depending on the efficacy of the vaccine in children aged less than five years. This graph assumes a vaccine with a cost of US$ 0.40 and an efficacy of 75% in adults and older children, and then examines the cost-effectiveness if the efficacy could be improved in young children to either 50% or 75% using data from the 1985 cholera vaccine trial in Bangladesh



The computer model suggests that there is a role of cholera vaccine in endemic areas, but that a rational decision about its use will depend on the availability of inexpensive vaccines (probably less than US$ 1.00) that provide a reasonable degree of protection, and that it be used in an area with an expected incidence of >1 case per 1,000. Thus, the proper use of vaccines in endemic areas will also depend on surveillance systems that can provide estimates of rates of cholera in the general population as well as in special sub-groups. Rates of cholera in age or socioeconomic sub-groups are important since the model also suggests that a vaccine might be targeted to sub-groups at high risk. For example, if children aged less than 15 years have high rates, the vaccine programme might be aimed at this group. Similarly, if a particular geographic area had high rates, the vaccine could be aimed at people of this area. In the future, when environmental surveillance provides an early warning of an impending cholera epidemic, the vaccine (along with other public-health strategies) might be provided on an urgent basis to minimize the impact of the epidemic.

This discussion has focused on the use of the killed oral cholera vaccine since this has been shown to be safe and effective in endemic areas. When live oral vaccines are also shown to be effective in these situations, their use will also be guided by similar cost-effectiveness considerations.

In conclusion, the study from Vietnam (1) does show that a vaccine programme is feasible, but we now have to learn when and how to produce and use these inexpensive oral vaccines.

REFERENCES

1. Thiem VD, Hossain MM, Son ND, Hoa NT, Rao MR, Canh DG *et al.* Coverage and costs of mass immunization of an oral cholera vaccine in Vietnam. *J Health Popul Nutr* 2003;21:304-8.

2. Legros D, Paquet C, Perea W, Marty I, Mugisha NK, Royer H *et al.* Mass vaccination with a two-dose oral cholera vaccine in a refugee camp. *Bull World Health Organ* 1999;77:837-42.
3. Infected areas as at 7 March 2002. *Wkly Epidemiol Rec* 2002;77:78-80.
4. Naficy A, Rao MR, Paquet C, Antona D, Sorkin A, Clemens JD. Treatment and vaccination strategies to control cholera in sub-Saharan refugee settings: a cost-effectiveness analysis. *JAMA* 1998;279:521-5.
5. Clemens JD, Sack DA, Harris JR, van Loon F, Chakraborty J, Ahmed F *et al.* Field trial of oral cholera vaccines in Bangladesh: results from three-year follow-up. *Lancet* 1990;335:270-3.
6. Glass RI, Becker S, Huq MI, Stoll BJ, Khan MU, Merson MH *et al.* Endemic cholera in rural Bangladesh, 1966-1980. *Am J Epidemiol* 1982;116:959-70.
7. Sack RB, Siddique AK, Longini IM, Jr., Nizam A, Yunus M, Islam MS *et al.* A 4-year study of the epidemiology of *Vibrio cholerae* in four rural areas of Bangladesh. *J Infect Dis* 2003;187:96-101.
8. Khan M, Shahidullah M. Cholera due to the E1 Tor biotype equals the classical biotype in severity and attack rates. *J Trop Med Hyg* 1980;83:35-9.
9. Clemens JD, Harris JR, Sack DA, Chakraborty J, Ahmed F, Stanton BF *et al.* Field trial of oral cholera vaccines in Bangladesh: results of one year of follow-up. *J Infect Dis* 1988;158:60-9.

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