Cholera: the need to translate research knowledge into effective preventive and control measures

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‘While we know about the pathogen and its pathogenesis at the basic level, why is this information not being translated into useful methods to prevent or control the spread of cholera?’

More than 150 years have past since *Vibrio cholerae*, the causative agent of cholera, was first described by Filippo Pacini and its water borne transmission was demonstrated by John Snow. In 1883, Robert Koch visualized the organism in Alexandria, Egypt and cultured it in Calcutta, India (now known as Kolkata). Nearly 70 years later, the toxin that caused cholera was discovered by SN De in Kolkata and by NK Dutta in Bombay, India (now known as Mumbai). The studies of De and Dutta, in effect, also proved Koch's postulate by replicating the disease in an animal model. These milestones in the biography of cholera were followed by the equally impressive discovery of oral rehydration solution (ORS) for the simple, but effective, treatment of cholera in the late 1960s, and between 1970 and 1990 dramatically brought down the mortality rate of this terrible disease. The following two decades have witnessed spectacular findings on the genetics and genome of *V. cholerae*, including determination of the whole genome sequence of the two chromosomes of an El Tor strain and of several more strains whose genome sequences are at the draft or near-completion stage. We have an intricate understanding of the nuances of *V. cholerae* in its ability to reside in the environment, orchestrate its virulence factors depending on the external milieu, and its ability to cross talk by quorum sensing and form social networks, termed biofilms. Clearly, the past decade has seen an information deluge on the pathogen. The March 2008 issue of the News Magazine of the American Society for Microbiology carries an article titled “The Ins and Outs of *Vibrio cholerae*” [1], which gives an impression that everything about cholera is known.

Contrast this information deluge on basic aspects of *V. cholerae* with what the annual cholera statistics released every year by the WHO has to say. The 2007 report presents a grim picture, with an overall global increase in the number of cases of cholera of 79% and an increase of 87% in the African continent in 2006 compared with the number of cases reported in 2005 [2]. WHO further states that almost every developing country is facing a cholera outbreak or the threat of an epidemic. The cholera epidemic has become uncontrollable and the incidences of global cholera have reverted back to the number of cases that had been attained in the early 1990s when cholera entered into the South American continent after 100 years and when the new serotype O139 of *V. cholerae* emerged. The actual burden of cholera is several magnitudes higher given that the global cholera statistics reported by WHO is an underestimate since many countries do not report cholera to WHO for fear of economic and trade embargos. Outbreaks of cholera in Africa and Asia are also on the rise with increasing case fatality rates and outbreaks dragging over longer periods than previously.

A question that stands out is why the burden of such a well studied organism is still so high and rising. Clearly, there is a significant gap between the basic scientific information acquired on cholera and the ability to use this knowledge to prevent, or at least control, cholera. Is all our research on cholera too esoteric and ‘not prioritized’ to bring about solutions to stem the growing burden of the disease? While we know about the pathogen and its pathogenesis at the basic level, why is this information not being translated into useful methods to prevent or control the spread of cholera? Obviously there is something amiss.

To control a cholera outbreak the critical first step is to lessen the burden of the disease. How does one alleviate the burden of cholera? The straightforward and time proven approach is to prevent the contamination of water and food. This is an approach that has successfully eradicated cholera in developed countries in Western Europe and in North America and Japan. Even if a case of cholera appears in these countries, transmission never occurs nor does the organism enter the environment because of a fool-proof system of

sanitation and the provision of safe drinking water. The challenge today, however, is to alleviate the burden of cholera in a poverty setting. In these settings, every cholera patient is a potential selector, amplifier and efficient disseminator of the organism and has the prospect of seeding the environment with a vast array of clones of the organism. Why has the strategy used in the aforementioned developed countries not been accomplished in countries such as India where the burden of cholera continues to be high despite being an emerging economy? Efforts are being made to provide safe drinking water and improve sanitation. The recent statistics on the supply of safe water and sanitation in India are, however, not appealing. Selected household characteristics in the recently (2005–2006) conducted National Family Health Survey that included 29 states (administrative divisions) in India indicate that a total of 25% (51% urban and 12% rural) have piped water and 45% (83% urban and 26% rural) have adequate toilet facilities [101]. This is still grossly inadequate for a country that holds one-sixth of the world's population and, therefore, the real numbers that do not have access to safe water and sanitation are staggering. At this pace, the provision of safe drinking water and sanitary facilities will take time especially in situations where there is a growing population and poverty burden. Rapid unplanned urbanization in the so-called rapidly emerging economies is not helping; in fact, it is exacerbating the situation. Therefore, the challenge today is to reduce the burden of cholera in an impoverished setting. Is that possible?

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As seen with other diseases, the use of a good public health tool, such as an effective vaccine, would dramatically improve the condition in an impoverished setting. Three oral cholera vaccines are currently available, which are safe, immunogenic and effective but these are still only used (and affordable) by travelers. One of these vaccines has been approved by WHO, and mass vaccination campaigns were conducted with WHO support [2]. Although these vaccines were developed and trialed several years ago, they are still not used nor are they licensed as public health tools in endemic and epidemic cholera

settings including India. There are many factors that have impeded the use of the cholera vaccine, including debates on protective efficacy, prohibitive costs, whether it should be a live or killed vaccine and, for reasons unknown, the lack of a conscious effort by policy makers in parts of the world where cholera is endemic.

The issue is do we implement a moderately efficient vaccine or wait till scientific research yields a 100% efficient vaccine (if that is possible). Our opinion is that a moderately efficient cholera vaccine should be placed into use as a public health tool given that it would play an important role in bringing down the burden of the disease, not to mention the lives that would be saved. Again, here we should take a leaf from the ORS story. The ORS that was first formulated and the ORS that is being used now have benefitted from several improvements. In fact, the search for a more efficacious and improved ORS is still on. The same philosophy for the use of a cholera vaccine would have helped – we could have implemented the vaccine into use several years ago. The parenteral cholera vaccine was discontinued in 1973 at the behest of WHO during the 26th World Health Assembly because it provided only limited protection of short duration and produced unpleasant side effects in many vaccinees. For almost three and a half decades, there has been no alternate to the parenteral cholera vaccine and the burden of cholera has not declined. Additionally, we have witnessed the emergence of the new cholera strain O139 and more recently a new El Tor variant that produces the classical cholera toxin [3]. These probably could have been stymied had we got a cholera vaccine into public health practice earlier.

Frantic international efforts are now underway to get one of these available cholera vaccines into public health use where they are most needed. Vietnam has taken an amazing lead on this and produced and tested a cheaper variant of the killed whole-cell vaccine, which when administered 2 weeks apart demonstrated 66% efficacy at 8 months. The Vietnam field trial concluded that an inexpensive, locally produced and effective oral cholera vaccine may be within reach of the limited healthcare budgets of poor countries with endemic cholera [4]. This vaccine is licensed only in Vietnam, but technology transfer to India supported by the International Vaccine Institute and the National Institute of Cholera and Enteric Diseases is underway [2]. A vaccine that is 66% efficacious is a great step forward rather than having no vaccine at all. A cholera patient in the wrong setting is capable of

spewing billions of organisms into the environment; therefore, imagine how much lesser contamination of the environment and therefore transmission would occur if we were able to reduce the case load by 66%. This, along with recently described herd protection of nonvaccinees attributed to cholera vaccine [5] would make an exponential difference and play a significant role in reducing global cholera burden.

In the absence of a public health tool, it is difficult to combat epidemics or implement long-term preventive measures. Take for example a resource-poor cholera endemic village setting in India. Endemic cholera periodically flares into an outbreak resulting in deaths. The Government promptly directs an epidemic team to investigate the outbreak. A team from a National Institute like ours quickly responds to the call and experts are dispatched. There is frantic activity at the outbreak spot; the etiologic agent, in these instances either *V. cholerae* O1 or O139, is detected, the epidemiologist announces a list of control measures including chlorinating water, the clinician manages the cases and aborts deaths, and before long the team is back to base satisfied that the outbreak has abated (which it would have anyway) and that some temporary changes were instituted. The next cholera season the cycle begins again and more often than not at the same places, which in effect shows that nothing much was accomplished by the investigating team apart from the management of cases at that given time. The emphasis here should be prevention and measures taken so that the outbreak does not recur in the same setting in the future.

We should begin to intensively inquire on how basic research on the organism and its pathogenesis can make inroads in preventing and controlling cholera in a poverty setting. The keyword here is 'poverty'. Again let us take ORS as an example; the discovery of ORS is steeped

into basic understanding of the physiological basis of electrolyte transport. This led to the development of a balanced salt solution, which in turn made history in the simplified treatment of acute secretory diarrheas and translated it into one of the greatest medical discoveries of the last century, in terms of lives saved. If we are unable to link these two together, then the distance between knowledge gained and knowledge successfully utilized is never going to merge. Let us not measure our successes on how quickly or on how many genomes are sequenced – let us begin to measure our success on how the knowledge on these genomes has allowed us to reduce the burden of the disease, by lessening the number of cases and by counting the number of lives saved. Let our basic sciences be specifically targeted to direct our research to areas such as control, transmission, prevention, and so on.

Finally, those in resource-poor settings who tend to view the use of vaccines with cynicism and ascribe unfounded fears, must change their mindsets. This attitude has to change if we are to make a dent in our appalling health statistics. For spiritual reasons, in our part of the world, we sometimes tend to sanctify poverty. We should instead begin to sanitize poverty (actually get rid of it) if we are to abolish diseases such as cholera, which thrive in these settings. We may know the 'ins and outs' of the organism, but the pathogen knows the ins and outs of where to strike and persist.

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Bibliography

1. Schild S, Bishop AL, Camilli A: Ins and outs of *Vibrio cholerae*. *Microbe* 3(3), 131–136 (2008).
2. World Health Organization: Cholera, 2006. *Weekly Epidemiol. Rec.* 82(31), 273–284 (2007).
3. Nair GB, Qadri F, Holmgren J *et al.*: Cholera due to altered El Tor strains of *Vibrio cholerae* O1 in Bangladesh. *J. Clin. Microbiol.* 4, 4211–4213 (2006).
4. Trach DD, Clemens JD, Ke NT *et al.*: Field trial of a locally produced, killed, oral

cholera vaccine in Vietnam. *Lancet* 349(9047), 231–235.

5. Ali M, Emch M, Von Seidlein L *et al.*: Head immunity conferred by killed oral cholera vaccine in Bangladesh: a reanalysis. *Lancet* 36, 44–49 (2005).

Website

101. International Institute for Population Sciences (IIPS) and Macro International. National Family Health Survey (NFS-3), 2005–2006, India: Key Findings. Mumbai: IIPS (2007). www.nfhsindia.org

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