Why is the global burden of cholera increasing?

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Cholera is an acute dehydrating diarrheal disease caused by toxigenic strains of *Vibrio cholerae* O1 or O139. The disease prevails in impoverished areas where safe drinking water is not available and where basic sanitary processes are compromised. Many impressive advances have been made in the past two decades on understanding the biology, pathophysiology, immunology, mechanism of pathogenesis, ecology and epidemiology of *V. cholerae* and of the disease cholera. *V. cholerae* has two chromosomes and the whole genome sequence of both these chromosomes of 24 strains of *V. cholerae* of different lineages isolated over the past 98 years have been explored and extensive genetic recombination via lateral gene transfer has been shown. The multi-factorial nature of virulence with cholera toxin playing the role of the 'conductor' in the virulence concerto and the intricacies of how virulence is regulated has been meticulously studied. The genetics of the cholera toxin prophage is known to its minute details. A variety of pathogenic islands, transmissible genetic elements and triggers that set these off are known. Two new variants, the O139 and El Tor *V. cholerae* carrying classical biotype cholera toxin genes have emerged and the genesis of these variants is now well known. We know that *V. cholerae* produces biofilm, shows the phenomenon of quorum sensing and we also know the intricacies of ecology of this climate sensitive pathogen. Much is also known about their aquatic existence and how the pathogen enters into a viable but non cultivable state in the environment and the biology and environmental factors and their role in the dynamics of cholera are relatively well understood.

However, recent statistics from the World Health Organization (WHO) clearly show that global trends in the incidence of cholera have increased steadily since the beginning of the millennium, when analyzed by 5-year periods. The African and Asian continents bear the brunt of endemic and epidemic cholera. Apart from Latin America, all other continents report either endemic or epidemic cholera and 12 countries reported imported cholera in 2008. A disturbing situation in Africa is the rising case fatality rates (CFR) due to cholera with 27 countries showing CFRs of above the 1% threshold in 2007. Zimbabwe offers the most recent example of how a country can be devastated when cholera strikes.

Despite all these advances in the basic understanding of the biology, ecology and epidemiology of the etiologic agent of cholera, why is the global trend in the incidence of cholera increasing steadily in many parts of the developing world? Obviously, acquisition of knowledge on the organism *per se* does not seem to be lowering the burden of the disease. Why this dichotomy? Is it that the knowledge acquired does not have direct relevance to reducing or eliminating the disease? Cholera is well known to be a disease of the poor with poverty and illiteracy generating the perfect socio-epidemiological conditions to cause and perpetuate the disease. Basically, poverty foster conditions that is optimal to transmit the disease from one person to another and to the community. As an efficient pathogen, *V. cholerae* has evolved special mechanisms like entering into a hyperinfectious state for about 6 hrs after being expelled by humans for optimizing its chances of entering another host. To combat the disease, there must be a paradigm

shift in addressing the problem. We need to generate knowledge which will allow us to eliminate the disease even in impoverished settings. We now have a cholera vaccine licensed in a country like India and the judicious use of the vaccines in conjunction with ready availability of safe water and improvement in sanitation in endemic areas and in epidemic situations would have a major role in aborting the transmission of infections and reducing the scourge of cholera over a period of time. The defining word here is poverty and how does one reduce a disease like cholera in a setting which has all the hallmarks of an ideal setting in an epidemiological and ecological sense. The next decade of research on cholera should redirect attention to these areas, if we want to make a dent in its global burden.