Editorial

Oral cholera vaccines – a call for action

Cholera remains one of the most dreaded diseases afflicting mankind. It can easily lead to death if adequate care is not provided immediately. Every year multiple outbreaks of cholera are reported in different parts of India affecting impoverished areas in the cities as well as remote areas with difficult access to health care. However, the number of cholera cases from India notified to the World Health Organization (WHO) is in few thousands annually, which is substantially lower than what is reported in literature. These discrepancies in reporting may be attributed to surveillance limitations, negative impact of such reports on tourism and trade and lack of proper incentives. A review of published reports from 1997 to 2006 showed that cholera was reported in 18 of the 35 States and Union Territories of India (National Institute of Cholera and Enteric Diseases, Kolkata, unpublished data). Of these, 11 including the capital, New Delhi, had cholera outbreaks reported for multiple years, affecting an ever increasing number of people. However, a survey of government officials in 2005 viewed cholera as less of a concern because of the decrease in mortality afforded by improved case management and availability of oral rehydration solutions and have cited water and sanitation improvement as their preferred methods for sustained cholera control.

While improved access to clean water and sanitation remain the mainstay of cholera control, these may not be achievable in the near future. Despite great strides in covering more communities with access to improved sanitary and water facilities, cholera continues to be a problem in several areas of the country. The licensure of a new-generation oral cholera vaccine (OCV) in India therefore provides a short to medium term solution for cholera control.

New-generation OCVs have been available internationally for more than two decades, and have been recommended by the WHO for the control of endemic and epidemic cholera. However, these have not been extensively adopted by developing countries. Currently, the only WHO-prequalified OCV is the recombinant B-subunit killed whole-cell vaccine (rBS-WC), Dukoral® (Crucell/SBL). Dukoral®, internationally licensed for individuals aged two years and older, is not licensed in India and is considered costly for routine use in public health settings. In addition, it requires at least two doses and needs to be ingested with a buffer solution. The other available OCV is the Vietnamese killed whole cell (WC) only vaccine. Following technology transfer from Swedish scientists, Vietnam produced a killed WC-only vaccine, which has only been used in high-risk cholera areas in Vietnam. Licensed locally since 1997, this vaccine contains both Vibrio cholerae O1 and O139, and provides 50 per cent protection for at least three years after vaccination. This vaccine has since been reformulated by the International Vaccine Institute (IVI), its production modified to comply with WHO and international regulations and its technology transferred to an Indian company.

Containing increased V. cholerae O1 lipopolysaccharide (LPS) content and more El Tor strains, this modified vaccine has been shown to be safe and immunogenic in Phase II clinical trials among adults in SonLa, Vietnam, and among children and adults in Kolkata, India. This vaccine has been evaluated in a placebo-controlled double-blinded randomized Phase III trial among >60,000 participants in Kolkata to assess protection of a two-dose regimen, which is conducted by the International Vaccine Institute, Korea, and the National Institute of Cholera and Enteric Diseases (NICED), a constituent Institute of the Indian Council of Medical Research (ICMR) in Kolkata. Interim analyses at the end of 2 years have shown promising results for both safety and efficacy.
No major side effects were reported, and protection was seen in all targeted age groups (68% protective efficacy among all individuals aged 1 yr and older). This vaccine is now licensed in India as Shanchol® (Shantha Biotechnics, Hyderabad).

The use of a similar WC vaccine also protects non-vaccinated individuals residing in areas with high vaccine coverage. Findings from a re-analysis of the Bangladesh trial of killed OCVs (both BS-WC and WC only) by the IVI indicated that these vaccines provided herd protection against cholera among those who were not vaccinated, including those who were too young to receive the vaccine, substantially increasing the public health impact of the killed OCVs. Modeling of the combined direct and herd protection from killed OCVs predicted near-extinction of cholera with population coverage rates as low as 50 per cent.

Cost-effectiveness studies for the modified oral killed WC cholera vaccine were also conducted. Assuming a one-time vaccination programme in which the WC vaccine was administered orally in two doses at a two-week interval, duration of vaccine protection was three years, and the vaccine provides 68 per cent direct protection for the first two years, costs were measured from the public perspective for three vaccination programme options: a school-based programme targeting 5-14 yr old children, a school-based programme targeting 1-14 yr old children, and a community-based programme targeting individuals 1 yr old and above. All three programmes were found to be cost-effective with the second one being the most cost-effective.

Injectable cholera vaccines have been used in India in the past, but have been abandoned for their reactogenicity and limited duration of protection. Cholera will not disappear in India soon and could extend to areas where it was previously not detected, especially with the predicted changes associated with global warming. The availability in India of the first low-cost oral cholera vaccine that complies with international production guidelines, that is easily administered, safe and effective, provides us the opportunity to act now, to lessen cholera disease and its accompanying economic and social burden. As the government continues to invest in improved water and sanitation, cholera vaccines should be considered as a supplementary short to medium tool for controlling the disease, especially for high risk areas.

At the meeting of the Strategic Advisory Group of Experts (SAGE) on immunization held in October 2009 at Geneva it was concluded that cholera control should be a priority in areas with endemic cholera since outbreaks can disrupt health systems. Vaccination in such areas should be targeted at high-risk areas and population groups. However, appropriate vaccination strategies should be left to the discretion of the individual countries. Pre-emptive or reactive vaccination should be considered to help prevent potential outbreaks or the spread of current outbreaks to new areas.

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NB: This editorial was written as a follow up to the Policymaker’s Meeting on Oral Cholera Vaccines in India held on 10 April 2009. The condensed proceedings of the meeting are available at: www.niced.org.in and www.ivi.org

References

