

High hopes for oral cholera vaccine

A trial of a new oral cholera vaccine in Kolkata is promising but, as Patralekha Chatterjee reports, a vaccine is only one weapon in the battle against the disease.

September 2006: phase III of a clinical trial of a bivalent, oral cholera vaccine was under way in a neighbourhood of Kolkata in eastern India. As in any clinical trial, this was a critical stage: the vaccine was being given to large groups of people to confirm its effectiveness, monitor side-effects and collect information that would allow it to be used safely.

More than 30 vaccination centres had been set up within the city's slums so that people did not have to go far to take the vaccine. Then, torrential rain lashed this city of more than 14 million people.

Such was the interest in the vaccine that people were not deterred by the weather. "It was indeed surprising to see the turnout even in that rain," recalls Dr Dipika Sur, Deputy Director of India's National Institute of Cholera and Enteric Diseases (NICED). "Sometimes, we would get frantic calls from our vaccination staff that the chairs and tables in our vaccination centres were floating."

Residents were enthusiastic about the vaccine trial as researchers had invested in two years of community education before the study started.

Dr Sujit Kumar Bhattacharya, medical officer with the World Health Organization's Regional Office for South-East Asia, emphasizes the importance of community consultation before a vaccine is introduced: "When we first developed the protocol, we knew scientifically we had a good, feasible-to-implement vaccine but it still had to be accepted by the people. We set up a little office in selected slums (where the trials eventually took place) in advance. At the start, people said 'give us clean water, sanitation' and so on.

"We held medical camps to treat other diseases, we held informal meetings with community leaders, we took into confidence the local imams (Muslim clerics) and even kept the National Human Rights Commission and the local police in the loop," says Bhattacharya, a former head of NICED.

The interim results of the phase III trial that started in Kolkata in

2006 were published recently. There were 20 episodes of cholera in the 52 212 people receiving vaccine and 68 episodes in the 55 562 people who received the placebo. "The results of the vaccine trial were 68% protection of all age groups two years after vaccination. Children aged five to 15 years had 88% protection. With a high burden of cholera in several areas of India, this was a very valuable finding," says Sur.

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For more than five years NICED has been working in Kolkata with scientists from the Seoul-based International Vaccine Institute to accelerate the introduction of this oral cholera vac-

cine, which has the potential to make a breakthrough in the battle against the disease.

John Clemens, Director-General of the International Vaccine Institute, says "our role has been to initiate the idea of internationalizing the vaccine, redesign the vaccine and provide technical and research support". Explaining the necessary partnership between the pharmaceutical company Shanta Biotechnics and the government, he adds, "Having NICED as a partner was critical, as was the formal approval of the Indian Council of Medical Research. The clinical trial was conducted in a population where NICED had already worked and had community relationships."

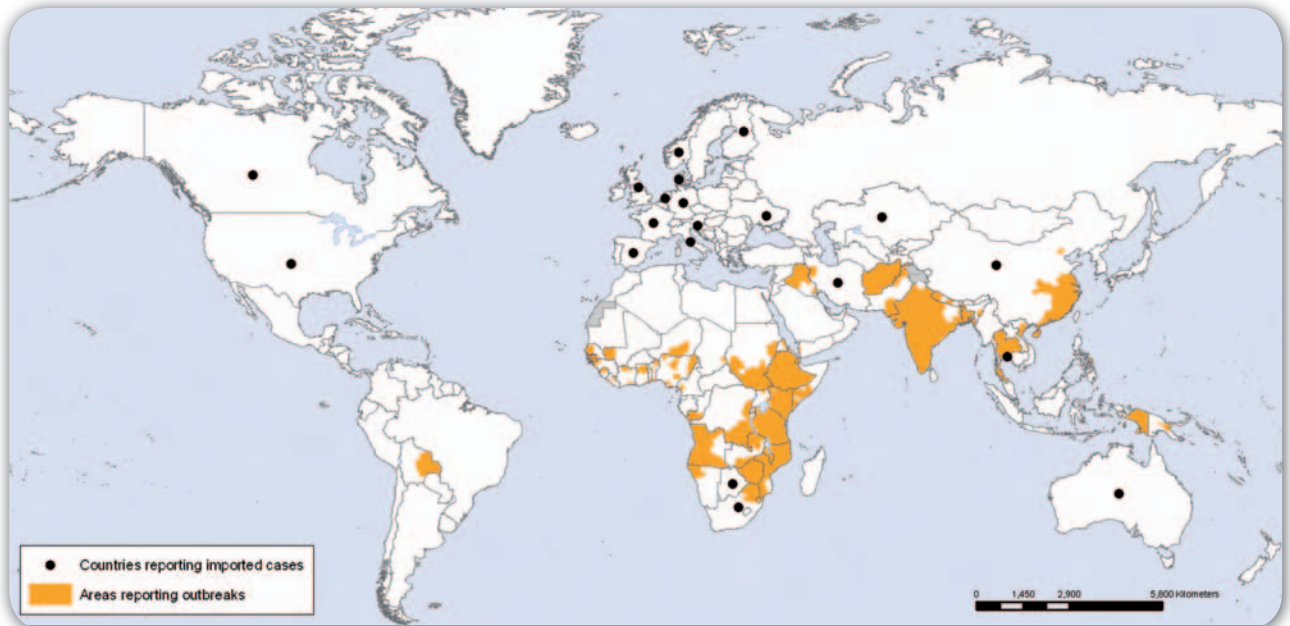
The new vaccine comes during a resurgence of the disease. Cholera is contracted by drinking water or eating food contaminated with the *Vibrio cholerae* bacterium and, without treatment, it can sometimes cause death within hours due to dehydration and shock.

Cases of cholera reported to WHO worldwide have increased steadily since 2000. From 2004 to 2008, a total of 838 315 cases globally were notified to WHO. This represents



Floods did not deter people from coming for the vaccine.

NICED



Cholera outbreaks and cases, 2007–2009 (as of October 2009).

a 24% increase compared with the 676 651 cases notified between 2000 and 2004.

However, the actual number of cholera cases is expected to be much higher because of the discrepancy resulting from underreporting and other surveillance system limitations, such as non-standardized case definition, or limited diagnostic means.

Cholera is on the rise, says Dr Claire-Lise Chaignat, head of WHO’s Global Task Force on Cholera Control, because there are “growing numbers of marginalized people, people moving from village to city, from high-risk to other areas; water and sanitation infrastructure and facilities are not able to keep pace”.

Even though oral cholera vaccines have been available for more than two decades, and have been recommended by WHO as a means of controlling cholera, they have not been extensively adopted by developing countries because of high cost, limited availability and the need for two doses.

Currently, the only WHO-prequalified oral cholera vaccine is the recombinant cholera toxin-B killed-whole-cell vaccine (rBS-WC), which is marketed as Dukoral and is internationally licensed for people two years and older. However, this vaccine is not

licensed in India, and is considered too costly and difficult to administer for routine general use.

Production of the vaccine in India followed a complicated trail of technology transfers from Viet Nam, which had in turn used a technology transfer from Sweden. Clemens explains the factors that favoured India as a choice for the manufacture of the vaccine.

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Dr Claire-Lise Chaignat

“For the vaccine to be acceptable for international use, it had to be manufactured in a country with a WHO-approved national regulatory authority and production had to comply with WHO standards. India’s national regulatory authority, the Drug Controller General of India, is WHO-approved and Shantha Biotechnics, the

producer, has already manufactured vaccines that have been prequalified by WHO,” says Clemens.

With the positive interim results of the phase III clinical trial in Kolkata, Shantha Biotechnics received all the necessary clearances for manufacture. The vaccine is presently being marketed in India under the name Shanchol.

The international drive to make cholera vaccines more widely available began with Diseases of the Most Impoverished programme and the Cholera Vaccine Initiative, both funded by the Bill & Melinda Gates Foundation and coordinated by the International Vaccine Institute.

The availability of an inexpensive, safe and effective vaccine that is easy to produce and administer will facilitate the role of vaccines in the control of cholera, but WHO’s Chaignat strikes a cautionary note. “It is good when countries with high cholera incidence can produce their own vaccine. We have high expectations from this vaccine, which is in the pipeline for pre-qualification by WHO. But a cholera vaccine is only an additional measure, not a substitute for safe water sources, proper sanitation and working with communities to encourage behavioural change to diminish the risks of infection.” ■