

unnecessary in most intubated and mechanically ventilated patients, and can be safely replaced by an on-demand approach, reserving studies for clinical indications. Whether an on-demand strategy is appropriate for individual intensive care units needs to be decided locally. In our view, an on-demand strategy should be adopted only if: skilled clinicians are available to promptly identify patients requiring chest radiography; images can be made and interpreted efficiently; and abnormalities can be acted on throughout the day. If these conditions are met, an on-demand strategy would seem justified and might lead to cost savings, decreased radiation exposure, and a greater diagnostic and therapeutic yield from the radiography.

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An affordable cholera vaccine: an important step forward

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The cholera epidemic in Zimbabwe, which has claimed over 4000 lives since August, 2008,¹ has refocused the world's attention on strategies to prevent cholera. Such devastating cholera outbreaks, increasingly common as a result of sudden movements of populations and natural disasters, represent the tip of the iceberg and add to the regular burden of endemic cholera. WHO reported 236 896 cholera cases worldwide in 2006, an increase of 79% over the previous year, although these figures are thought to represent only 5–10% of actual cases.² For regions of the world beset with endemic cholera, such as southeast Asia and eastern and northwestern Africa, better sanitary conditions and clean drinking water are the solutions for preventing seasonal cholera epidemics. However, these improvements have not taken place rapidly enough, further highlighting the growing need for a safe, effective, and affordable cholera vaccine that can be deployed in cholera-endemic regions.

In *The Lancet* today, Dipika Sur and colleagues³ report the results of a phase 3 trial of a killed oral cholera vaccine in a cholera-endemic region of India. The vaccine is a redesigned version of a proven safe⁴ and effective⁵ bivalent (contains O1 and O139 serogroups of *Vibrio cholerae*) cholera vaccine, which is produced and deployed in Vietnam. The current Indian vaccine they studied is based on the Vietnamese vaccine,⁶ but with strain changes and other modifications designed to meet WHO production standards and removal of all cholera toxin.

Today's study evaluated the redesigned vaccine for efficacy against cholera in more than 65 000 individuals, including children older than 1 year, living in an urban slum in India. The investigators randomised clusters of households to receive either two doses of the vaccine or the placebo. They report the results of a planned interim analysis of the first 2 years of follow-up. The vaccine did not increase the risk of side-effects

compared with the placebo and showed 67% efficacy in the entire population (99% CI lower boundary, 35%). In cholera-endemic areas, due to the development of immunity in adults, children younger than 5 years are most affected. Importantly, the evaluated vaccine conferred 49% protection (95% CI lower boundary, 6%) against cholera in children aged 1–5 years, although the effectiveness of the vaccine dropped (efficacy 40%; 95% CI lower boundary, –3%) if the vaccine was not given in two doses or was incompletely ingested (intention-to-treat analysis), as might happen during mass immunisation programmes.

In 2001, WHO recommended the only internationally licensed cholera vaccine, a whole-cell vaccine with recombinant cholera toxin B subunit (WC/rBS), for use in those at risk in endemic regions. However, the high cost of the WC/rBS vaccine (it is sold for about US\$20 per dose in Bangladesh) precludes its deployment as a public health strategy in poor cholera-endemic countries. The Indian vaccine evaluated by Sur and colleagues has two main advantages over the WC/rBS vaccine, namely ease of administration (no requirement for coadministration of buffer) and lower cost. Their study provides important evidence of efficacy in adults and children of a cheaper, internationally licensable alternative to the WC/rBS vaccine that might be a viable candidate for deployment as a public health approach in cholera-endemic regions.

Today's encouraging results must be tempered by cautious optimism as results from longer follow-up for evidence of lasting protection must be reviewed before this current vaccine is recommended as an alternative to the expensive WC/rBS. The protection conferred by the WC/BS (similar in immunogenicity to the licensed WC/rBS vaccine) vaccine is lost after 2 years in children aged under 5 years,⁷ even after administration of three doses. While the efficacy of the Indian vaccine tested in Sur and colleagues' study is similar to that attained by the currently licensed WC/rBS and the WC/BS vaccine, we must keep in mind that these vaccines were last evaluated in controlled clinical trials between 15 and 20 years ago.^{7,8} The dependence of vaccine efficacy on local ecological determinants,⁹ along with the changing nature of cholera's epidemiology, make a comparison of the results of today's vaccine trial against the results of vaccine trials from more than 15 years ago difficult,



prompting the need for direct comparison of the Indian vaccine and WHO's recommended vaccine (WC/rBS).

Some of the other questions that need to be answered for the Indian vaccine, either from Sur and colleagues' study or future studies, include the evaluation of herd protection, as observed in the reanalysis of the 1985 Bangladesh trial of killed oral cholera vaccines,¹⁰ vaccine efficacy in cholera-endemic regions of Africa with higher incidence and severity of cholera than the urban slums of Kolkata, and the efficacy of a single dose and annual booster doses of the vaccine compared with the currently administered two vaccine doses. Although the above questions need additional study, today's report provides promise of a cholera vaccine that is not only effective but also affordable, and which might be the first major step in the deployment of a cholera vaccine for mass immunisation in cholera-endemic areas.

The most impressive aspect of this Indian vaccine is the story of its development. The vaccine was initially licensed by the Vietnamese Government after technology transfer from Sweden. Later, scientists from the International Vaccine Institute in Seoul, with funding from the Bill & Melinda Gates Foundation, worked with the Vietnamese manufacturer, VaBiotech, to revise the strain composition of the vaccine, improve the manufacturing process, and transfer the reformulated vaccine to a WHO-approved Indian manufacturer that could produce the vaccine for

international use. The story of the development of this vaccine underlines the success of an international collaborative effort of public-private partnership and academic research organisations when provided with adequate funding, infrastructure, and support. This success story ought to be an example for other vaccine initiatives, especially against malaria and HIV, to similarly engage industry and academia towards solving an urgent public health need.

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Dengue in Cuba: research strategy to support dengue control

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In recognition of the importance of research for human health, Cuba has been working hard to improve its capacity to face infectious diseases. Among these, dengue, an arthropod-borne disease caused by dengue viruses and transmitted by the *Aedes aegypti* mosquito, occupies a major position, when we consider that Cuba is surrounded by endemic countries and thus at risk of virus introduction.

The characteristics of the prevention programme for dengue, the continuous process of human-capacity building, and the development of basic and implementation research have been fundamental to keep the country free of dengue. Although sporadic epidemics have been reported, they were eliminated.¹

Epidemiological, clinical, and virological studies have improved our knowledge about dengue. The role of secondary infection by a different dengue serotype, reported in Thailand and others countries² as a risk factor for severe illness, has been confirmed in Cuba.^{1,3,4} Also, three important discoveries have been reported: the increase in disease severity corresponding to the longer interval between first and second dengue infections;³ the existence of a human dengue resistance gene (black people are highly resistant to severe dengue);^{4,5} and a rapid increase in the severity of dengue disease as the epidemic advances.^{1,4,6}

Early recognition of the role of the host, the virus, and the epidemiological conditions is important to explain epidemics of dengue haemorrhagic fever.⁴ Relevant factors are the report of some chronic diseases as risk factors for severity,^{1,4} the recognition of warning signs for severe illness, and the association of some viral sequences with clinical outcome.⁷ Other scientific findings have implications for pathogenesis, case management, and vaccine development, such as dengue haemorrhagic fever 20 years after the primary dengue infection,^{1,3,7} the study of gene polymorphisms (such as HLA and FcγRIIIa) and their association with susceptibility or resistance to dengue infection,⁸ and the role of humoral markers and cellular immune mediators in the course of the illness.⁹

Improvement of the diagnosis of dengue is another important research area. The serological and molecular diagnostic techniques that have been developed, including the Cuban ultramicro ELISA for specific IgM detection,^{10,11} have allowed the country to be self-sufficient. The Cuban laboratory network with its serological capacity and the reference centre at the Institute of Tropical Medicine support the national laboratory surveillance.

For a vaccine, two recombinant candidates (chimeric protein domain III fused to p64k of *Neisseria meningitidis* and a fusion protein domain III capsid from