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Capacity of developing country NRAs key to accelerated introduction of upcoming dengue vaccines

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At least one dengue vaccine could be licensed within the next 4 years, as manufacturers are speeding up the development process for multiple dengue vaccine candidates in collaboration with health authorities and developing countries to expedite the necessary testing, clinical trial design, and licensure, a team of leading scientists said.

"A number of important issues have been identified for regulatory review of dengue vaccines, while plans are being developed to provide appropriate training and capacity building for developing countries' national regulatory authorities (NRA) in endemic countries to accelerate the licensure process when a new dengue vaccine becomes available," the scientists said in their study published in the February 22 issue of *PLoS Medicine*.

The study was conducted by the Pediatric Dengue Vaccine Initiative (PDVI) in cooperation with the World Health Organization. The PDVI, a product development partnership funded by the Bill & Melinda Gates Foundation, was recently succeeded by the Dengue Vaccine Initiative Consortium hosted by the International Vaccine Institute (IVI), a Seoul, Korea-based international organization.

Dengue affects over 3.6 billion people in 124 countries, or 55% of the world's population. It causes about 34 million cases of clinical dengue fever with more than 6% of cases developing more serious forms such as

dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), both of which can result in death. There are no effective drugs to treat dengue infection. Vector control for the mosquito vector, Aedes aegypti, has not proven to be sustainable or highly effective.

Dengue is prevalent only in tropical countries where the vector is common. Clinical trials to assess the safety and efficacy of dengue vaccines must therefore be carried out in these developing countries, and it is likely that the first licensure of dengue vaccines will occur there.

Dengue diseases are caused by four related viruses. In most countries, one virus tends to dominate during a season, but is replaced by other viruses over several years. Thus, a dengue vaccine must be effective against all four viruses (i.e., tetravalent). Because a dengue vaccine should be tetravalent in nature and provide protection against all four dengue serotypes, regulatory agencies need to address additional issues associated with multivalent vaccines such as interference between the vaccine serotypes.

Dengue affects a wide age range from infants through young adults. A dengue vaccine will have to be evaluated in diverse populations in both the Americas and the Asia Pacific region and delivered in national immunization programs to infants and in "catch-up" programs to older age groups.

In recognition of these and other complications, there is high priority to ensure that developing countries have the capability to undertake appropriate regulatory review of proposed clinical studies and of applications for licensure, the scientists said. "It is important that the NRAs of these developing countries have the information, training, and capabilities to review and approve applications to undertake clinical trials and eventually, if appropriate, license dengue vaccines," said Dr. Richard Mahoney, Coordinator for Policy & Access of DVI.

"Involvement of leading agencies, including the US Food and Drug Administration and the European Union European Medicines Agency for the Evaluation of Medicinal Products (EMA), can be helpful in assuring a high level of regulatory review."

Dengue vaccines have been under development since the 1940s, but due to the limited appreciation of the global dengue disease burden and of the potential markets for dengue vaccines, industry's interest languished throughout the 20th century. However, in recent years the development of dengue vaccines has accelerated dramatically.

"It is fortunate that there are several vaccines under clinical development, because there is no certainty as to which, if any, of the candidate vaccines will prove to be safe and efficacious," said Dr. Liliana Chocarro, formerly of WHO and a leading expert on vaccine regulation in developing countries. "Also, wide access will depend upon a competitive environment in which several manufacturers are supplying vaccines."

Vaccines in clinical development include four live attenuated vaccines, one inactivated vaccine, and one subunit vaccine. The vaccines under development by GlaxoSmithKline and sanofi pasteur have completed Phase 1 testing and initial Phase 2 (Phase 2a) testing, respectively. "Notably, the sanofi pasteur vaccine entered expanded Phase 2 (Phase 2b) testing in 2009 in Thailand and could be licensed as early as 2015," said Dr. Luiz da Silva, the incoming Director of DVI but who is not a co-author of the study. GlaxoSmithKline has recently launched a program to develop an inactivated vaccine. The vaccine (dengue-dengue chimera with gene deletion) developed by the US National Institutes of Health (NIH) entered tetravalent Phase 1 trials in 2010. The subunit vaccine developed by Hawaii Biotech (now owned by Merck) entered Phase 1 testing in 2009.