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Cost of production of live attenuated dengue vaccines: A case study of the Instituto Butantan, Sao Paulo, Brazil

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ABSTRACT

Background: A vaccine to prevent dengue disease is urgently needed. Fortunately, a few tetravalent candidate vaccines are in the later stages of development and show promise. But, if the cost of these candidates is too high, their beneficial potential will not be realized. The price of a vaccine is one of the most important factors affecting its ultimate application in developing countries. In recent years, new vaccines such as those for human papilloma virus and pneumococcal disease (conjugate vaccine) have been introduced with prices in developed countries exceeding $50 per dose. These prices are above the level affordable by developing countries. In contrast, other vaccines such as those against Japanese encephalitis (SA14-14-2 strain vaccine) and meningitis type A have prices in developing countries below one dollar per dose, and it is expected that their introduction and use will proceed more rapidly. Because dengue disease is caused by four related viruses, vaccines must be able to protect against all four. Although there are several live attenuated dengue vaccine candidates under clinical evaluation, there remains uncertainty about the cost of production of these tetravalent vaccines, and this uncertainty is an impediment to rapid progress in planning for the introduction and distribution of dengue vaccines once they are licensed.
Method: We have undertaken a detailed economic analysis, using standard industrial methodologies and applying generally accepted accounting practices, of the cost of production of a live attenuated vaccine, originally developed at the US National Institutes of Health (National Institute of Allergy and Infectious Diseases), to be produced at the Instituto Butantan in Sao Paulo, Brazil. We determined direct costs of materials, direct costs of personnel and labor, indirect costs, and depreciation. These were analyzed assuming a steady-state production of 60 million doses per year.
Results: Although this study does not seek to compute the price of the final licensed vaccine, the cost of production estimate produced here leads to the conclusion that the vaccine can be made available at a price that most ministries of health in developing countries could afford. This conclusion provides strong encouragement for supporting the development of the vaccine so that, if it proves to be safe and effective, licensure can be achieved soon and the burden of dengue disease can be reduced.

1. Introduction

Dengue is the world's most important arboviral disease affecting 124 countries with populations of over 3.6 billion people. It results in 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) which can result in death [1]. There are no effective drugs to treat dengue infection [2]. Vector control for the mosquito vector, *Aedes aegypti*, has not proven to be sustainable or highly effective [3]. Because the mosquito breeds in open water containers found often in populated areas and the mosquito is a day-biter, the disease is more prevalent in urban areas and infection occurs most often during the day.

Dengue presents with fever, retro-orbital pain, myalgia, and petechia. Symptoms may last for 10–14 days and may progress to DHF and DSS – conditions having mortality rates as high as 10% of cases. While there are no therapeutic drugs, modern intensive care can reduce case fatality rates to less than 1%. However, there

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are no reliable laboratory diagnostics for the first four to five days of infection thereby limiting the ability of physicians to identify at-risk patients early in the disease. Unfortunately, patients may appear to be recovering around day 6 with falling temperatures only to develop DHF or DSS in a matter of hours [4].

With the significant morbidity and mortality of dengue, there is an urgent need to develop safe and effective dengue vaccines. 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 in these countries.

Dengue is caused by four related viruses (DENV1, DENV2, DENV3 and DENV4). Dengue epidemics have annual cycles where the highest incidence occurs during the rainy season when mosquito populations increase. A single dengue serotype tends to dominate during a season, but this dominant serotype varies from season to season. Epidemiological studies have established that the risk for more severe dengue illness is higher following a second infection with a DENV serotype different from primary infection [5], although severe illness can also occur following primary infection. This potential immune enhancement (antibody dependent enhancement – ADE) resulting from prior infection is thought to increase virus replication, which has been shown to correlate with disease severity [6]. Although severe dengue illness can occur with a third or fourth DENV infection, this risk appears to be very low [7]. Thus, a vaccine against dengue must be effective against all four viruses to ensure adequate protection. If a candidate vaccine cannot induce immunity against all four viruses, there is the theoretical possibility of an adverse immune response in individuals who are left unprotected against all four viruses. The challenge to develop a tetravalent vaccine is compounded by the reality that a balanced tetravalent response is often unattainable, possibly due to interference among the viruses in a live-attenuated tetravalent vaccine. These technical challenges in vaccine development are further increased by the lack of an animal model for dengue infection and disease [4].

Another consideration in the development of dengue vaccines is that dengue affects a wide age range from infants through teenagers to young adults. Older adults often have high levels of natural immunity or infection leads to less severe disease. Therefore a licensed dengue vaccine will have to be delivered not only in national immunization programs to infants but also in catch-up programs in older age groups.

2. Status of vaccine development

Vaccines under development include four live attenuated vaccines, one subunit vaccine, and one purified inactivated vaccine. The developers are GlaxoSmithKline (GSK), InViragen, Merck, U.S. NIH (NIH), and Sanofi Pasteur. The NIH has licensed its live attenuated vaccine candidate to four developing country producers – Biological E (Hyderabad, India), Instituto Butantan (Sao Paulo, Brazil), Panacea Biotec (New Delhi, India), and Vabiotech (Vietnam). GSK has two candidates: one a traditional live attenuated vaccine prepared by cell passage and the other a purified inactivated vaccine. However, following Phase 2 evaluation of its live attenuated vaccine candidate, GSK has suspended further development of this live vaccine candidate while pursuing its inactivated vaccine. The Merck candidate is a subunit vaccine and a monovalent component entered Phase 1 trials in 2010. The Inviragen, NIH, and Sanofi Pasteur candidates are live attenuated vaccines derived by various reverse genetic techniques. The Inviragen vaccine is comprised of chimeric viruses based on a PDK-passaged DENV2 background and a tetravalent formulation of the vaccine entered Phase 1 trials in 2010. Both monovalent and tetravalent mixtures of the vaccine developed by NIH have been in Phase 1 testing under the auspices of NIH and vaccine components are described below. The Sanofi Pasteur vaccine is comprised of chimeric viruses based on the 17D yellow fever virus vaccine background and the tetravalent formulation entered expanded Phase 2 (Phase 2b) testing in January 2009 and Phase 3 in late 2010. If the Phase 2b evaluation of the Sanofi Pasteur vaccine indicates that the vaccine is safe and effective, it is possible that licensure of this vaccine may occur as early as 2014. For a recent review of dengue vaccine development, see Whitehead [8] The Laboratory of Infectious Diseases at NIH has used reverse genetics to introduce defined attenuating deletion mutations in the DENV4 and DENV1 viruses with a 30 nucleotide deletion (Δ30) in each virus. These deletions achieved a desirable balance between attenuation and immunogenicity in monkeys and humans. The deletions did not yield satisfactory results for DENV2 and DENV3. To create vaccine viruses for these latter two viruses, the NIH created chimeras with DEN4Δ30 as the background and inserted selected genes (prM and E) from DENV2 and DENV3 into the DEN4Δ30. These chimeras are referred to as DEN2/4Δ30 and DEN3/4Δ30. As DEN3/4Δ30 has also not achieved balanced attenuation and immunogenicity two additional DEN3 vaccine viruses were created, DEN3-3′D4Δ30 and DEN3Δ30/31. DEN3-3′D4Δ30 vaccine virus was constructed by replacing the entire 3′UTR of a DENV3 virus with the 3′UTR of the live attenuated vaccine candidate DEN4Δ30. DEN3Δ30/31 vaccine virus was constructed by further mutating the DEN3-3′UTR by combining the Δ30 deletion with an additional 31 nucleotide deletion in the DEN3 3′UTR. Several patent applications have been submitted concerning these constructs and the NIH has licensed the patents and other intellectual property to the above-mentioned companies. These licensees seek to develop commercial production capabilities, take the vaccine through clinical evaluation and licensure, and introduce the vaccine into various markets.

3. Instituto Butantan

The Instituto Butantan is controlled by the Secretary of Health of the State of Sao Paulo, Brazil, and is responsible for the production of more than 80% of the vaccines used by the Brazilian National Immunization Program.

The Federal Government of Brazil has a policy to encourage domestic production of vaccines acting as the major consumer of vaccines produced by Instituto Butantan and BioManguinhos – FioCruz, Rio de Janeiro. Although Butantan has the goal to supply the Brazilian immunization program, it may have the capacity to export dengue vaccine to neighboring countries as it already does with some vaccines.

4. Potential market and projected production capacity for dengue vaccines in Brazil

Preliminary estimates of the potential market for dengue vaccines in a number of GAVI-eligible and GAVI non-eligible countries have been prepared [9,10]. The results of the computations for the specific case of Brazil are summarized here.

The authors assumed that the routine immunization will be limited to a cohort of the 1–2 year old age-group in the first five years, and catch-up immunization strategies will adopted for high risk groups. Three options are used for catch-up immunization: immunizing 2–5, 2–10, or 2–15-year-old children. Since a dengue vaccine will be given after the first year of life, they estimated dengue vaccination coverage to be the same as measles vaccine coverage. Further, they assumed that expected coverage for routine immunization of the 1–2-year-old cohort will increase from 70% to 80%