

Key Messages:

- The successful development of a dengue vaccine will lead to the requirement for the establishment of sufficient production capacity to meet large projected needs.
- Producers in industrialized countries are likely to play a lead role in supply of dengue vaccines, but recently the proportion of vaccine supplied by developing countries producers has risen dramatically.
- Vaccine producers in developing countries have a number of capabilities and recently have been engaged in vaccine development from preclinical studies to licensure.
- Progress in dengue vaccine development has been promising and developing country manufacturers are actively involved, especially in Brazil, India and Vietnam.
- Development of a dengue vaccine faces many challenges including the need to be effective against the four dengue serotypes, i.e. it must be tetravalent.
- Developers may abandon or find obstacles in dengue vaccine development because of changed priorities, need to develop costly dengue-specific capabilities such as in diagnostics, lack of reliable demand projections, and obtaining purchase and delivery commitments.
- To overcome these obstacles there is a need for increased financial resources, for support to build up scientific and technical capability in developing country manufacturers, to increase human and logistical resources for manufacture,
- The manufacture of dengue vaccine by either industrialized or developing country manufacturers should be a part of a global access strategy created and executed by a diverse set of global partners.
- Developing country manufacturers will be an important component in ensuring the availability of safe, effective, and affordable dengue vaccines.



A program of



In depth examination of important issues for the development and introduction of DENGUE vaccines

The manufacture and supply of dengue vaccine

Don Francis, Don Douglas, Richard Mahoney

Ultimately, the elimination of dengue virus-related morbidity and mortality will depend on the development and delivery of safe and effective vaccines that prevent infection from all four dengue virus serotypes. Following successful development of such a product, the next step for a successful dengue control program will be large-scale vaccine manufacture. Meeting the huge projected public- and private-sector demand¹ for a new dengue vaccine will be challenging. Indeed, the effort and technical complexity required for manufacturers to move production from the small clinical research scale to world-wide commercial scale will be considerable. Historically, there have been immense delays in accomplishing this important step in disease control programs. For example, the time from when a vaccine is first licensed in a industrialized country to the time the majority of those in need in the developing world have access to the vaccine can be as long as 20-30 years^{2,3}. Scale-up of manufacture is only one factor causing this delay, but it can be an important factor as witnessed by the limitations in supply of the seven-valent pneumococcal conjugate vaccine from Wyeth⁴. For dengue, several factors point to the real possibility of helping to speed up the progression of the vaccine from research mode to large-scale manufacture and into public immunization programs, or 'from bench-to- community', by encouraging manufacture in both industrialized and developing countries.

Background

Industrialized world producers: There are relatively few global producers of vaccines in the industrialized world. These producers have traditionally carried out the bulk of the development of new vaccines and have supplied both industrialized and developing country markets. These companies have evolved from national, and in some cases state-owned, companies into multinational pharmaceutical conglomerates. They are fully integrated, highly-capitalized firms with extensive marketing and distribution networks⁵. Their products account for the majority of the revenue and profits in the vaccine industry. These large multinational companies accounted for only 43 percent of the vaccine doses supplied to the GAVI Alliance in 2008⁶.

Developing country producers: In the past two decades, developing country vaccine producers have dramatically increased the capacity, quality, and distribution of their vaccines. Previously, the vaccines produced in the developing world tended to be older, out-of-patent and often monovalent products which lent themselves to production in large volume, at significantly lower cost than newer, multivalent vaccines. More recently, a handful of developing country vaccine producers, particularly in India, Brazil, Indonesia and Vietnam, have begun developing new vaccines. They have evolved from non-good manufacturing practice (GMP) compliant companies with little or no capacity for development of new vaccines to large-scale producers of high-quality vaccines in

modern plants with highly-qualified scientific and technical personnel⁷.

Increasingly, some of these companies have now taken on research and development (R&D) for the next generation of vaccines. They expect to develop, and are prepared to produce, new vaccines from initial research through to final product. This change has resulted from several intersecting forces:

- 1) Increased money available to the vaccine market from the GAVI Alliance,
- 2) Recognition by the companies of the importance of having a strong R&D pipeline,
- 3) Increased competence (and confidence) in process development
- 4) Ability to access new technologies⁸

It is clear that vaccines for the world's annual birth cohort of over 150 million will increasingly be produced in the countries that use the greatest proportion of the global vaccine supply⁹. Because manufacturers in these countries are producing high quality-low cost vaccines for a variety of diseases, the competitive environment is changing. These new entries into the market of modern vaccines will clearly change the competitive playing field for developing country vaccines. It is logical and necessary for international organizations to encourage, assist and support vaccine production in developing countries in order to share the development challenges and risks of new and improved vaccines including dengue vaccines.

Dr. Francis is the Executive Director and Founder of Global Solutions for Infectious Diseases, a not-for-profit foundation dedicated to developing and testing vaccines and other products for less developed parts of the world. Beginning with the U.S. CDC, he has worked focused on vaccine-preventable diseases, such as measles, cholera, smallpox, and hepatitis B. He directed the WHO's Smallpox Eradication Program in Sudan and the state of Uttar Pradesh in Northern India. His hepatitis B vaccine work included conducting Phase III trials among gay men in the U.S. and among infants born to carrier mothers in China. He served as a member of the WHO team investigating the world's first outbreak of Ebola virus in 1976 and worked on HIV/AIDS since its emergence in 1981, including initially directing the AIDS laboratory at the CDC and worked closely with the Institut Pasteur to identify the causative virus. Beginning in 1996 he was founder and president of Vaxgen, a company devoted to developing an AIDS vaccine that has recently shown promise in a prime boost trial.



Progress towards dengue vaccines

Recently, the increased appreciation of the immense epidemiological impact of dengue virus infection and the availability of funding from sources such as the Bill & Melinda Gates Foundation have led to greater priority for the development of safe and effective dengue vaccines. This appreciation, linked to a better understanding of dengue virus immunity and the progress in virological genetic manipulation of vaccine candidate strains, has markedly improved the prospects of actually developing and delivering effective vaccines in the future¹⁰. The better understanding of the importance of dengue coupled with scientific advances have encouraged companies capable of developing dengue vaccines, both in industrialized and developing countries to invest increasing resources towards dengue vaccine R&D. Moreover, public health experts, government-funded vaccine research and not-for-profit vaccine development organizations have increasingly joined forces to maximize the chances of both developing and fielding a preventive dengue vaccine.

In recent years, there have been increasing collaborative efforts between industrialized country institutions and developing country vaccine developers. This is taking place not only in the area of field study of vaccine efficacy using European- and North American-developed products, but importantly, in the arena of vaccine development itself. Vaccine companies in Brazil, India and Vietnam have taken on large projects of bench-to-field dengue vaccine development (Table 1). These companies, with state-of-the-art facilities, appear to have the potential to successfully bring these products forward.

Yet there are challenges ahead in these largely uncharted waters. The most recently licensed products from these companies have been those, like hepatitis B vaccine, that have had well traversed development pathways. With these vaccines, the producer's primary activity has been duplicating previously developed production pathways. But developing an effective vaccine for dengue is different. Besides the general challenges

associated with developing any new vaccine, there are dengue-specific issues that make such development even more challenging. First, a dengue vaccine must be able to protect against all four circulating virus serotypes (DEN 1-4). This is because it is not possible to predict which of the four viruses may circulate at any one time, and all four viruses are endemic in several countries. Also, the antibodies induced by vaccine against only one serotype are postulated to potentially cause more severe disease when a secondary or tertiary live virus infection occurs with a heterologous virus. Thus, the vaccine has to be tetravalent and should induce long-lasting protective antibodies to all four serotypes. Development of immunogenic monovalent live attenuated dengue vaccines has been accomplished. But formulating them into a tetravalent vaccine may result in interference between the components of the tetravalent vaccine resulting in failure to elicit tetravalent seroconversion and protection. To achieve optimum immunogenicity of the tetravalent vaccine, extensive formulation studies will likely be required. In addition, there is no reliable animal model which mirrors the clinical syndrome of the dengue virus infection of humans (although some recent important progress has been achieved¹¹), and correlates of protection are not yet clearly defined. As a result, extensive human clinical testing and long term follow-up will be required to evaluate the immune responses and safety of tetravalent vaccines.

The development of safe and effective dengue vaccines by developing country producers will take time and substantial resources. Independent, expert assessment of these companies has been conducted by Global Solutions for Infectious Diseases under contract to the Pediatric Dengue Vaccine Initiative (PDVI), and it has been concluded that the probability of technical success is high. Yet, there is the need for ongoing technical, operational, and regulatory assistance to ensure that the development goes smoothly and obstacles are overcome as they are encountered.

The estimated at-risk population for dengue is 3.6 billion people¹², and thus the estimated demand for safe and effective dengue vaccine is large¹. To help assure a sustainable and sufficient supply of dengue vaccine, it is important to have a number of manufacturers. Having candidate vaccines in development from European, American, Brazilian and Indian companies will both increase the chances of success and ensure the availability of production capacity to produce and supply these products to regions of high endemicity.

There are other reasons to encourage multiple manufacturers. Despite strong technical capabilities among the several companies in both industrialized and developing countries developing dengue vaccines, there is no guarantee that any will succeed in bringing a product to market. Indeed,

Don Douglas is a Senior Program Officer on Vaccine Access for the Pediatric Dengue Vaccine Initiative (PDVI) at IVI where he convenes the Dengue Prevention Boards in the Americas and Asia-Pacific, and conducts policy studies on dengue vaccine introduction. Previously he served as Country Director for PATH (Program for Appropriate Technology in Health) in Thailand, and Indonesia where he led ground breaking efforts to understand the social determinants of HIV transmission, introduced a range of immunization and MCH technologies and managed Hepatitis B Vaccine Model Programs and a Phase 4 Clinical trial of Haemophilus B Influenza vaccine that led to national immunization. He also served as CEO of Sabin Vaccine Institute (SVI), and worked with the Developing Country Vaccine Manufacturers Network (DCVMN).

there is a good likelihood that some will fall by the wayside because of lack of either efficacy or safety. Moreover, some products, although proven to be effective, may initially be priced at a level that would make it difficult for many developing countries to purchase.

Financial analysis has shown that substantial investments are needed from the international donor community in order to reduce the time lag between availability of vaccines in industrialized countries and their availability in developing countries.

Moreover, such investments help to stimulate R&D of new vaccines such as those for dengue¹³. In most of the developing world, the limitations to delivery of a new vaccine include insufficient delivery infrastructure, and lack of capacity among vaccine producers to meet demand. Here, the most important limitation may be the inability of governments to finance the purchase of new vaccines. Analysis of the introduction of new vaccines such as hepatitis B has shown that it "is economics and not epidemiology which dictates introduction of the vaccine into national immunization programs"¹⁴.

Developer	Manufacturer Sponsor	Approach	Formulation	Trial Status
Walter Reed Army Institute of Research (WRAIR)	GlaxoSmithKline	Cell culture passage of clinical isolates	Tetravalent	Phase 2, adults and children
Walter Reed Army Institute of Research (WRAIR)	GlaxoSmithKline and Oswaldo Cruz Institute	Purified inactivated vaccine	Tetravalent	Preclinical
Acambis (now owned by sanofi pasteur)	sanofi pasteur	Chimeric infectious clones. Yellow fever vaccine virus (nonstructural) + dengue envelope & preM genes	Tetravalent	Phase 3, children
U.S. National Institutes of Health (NIH)	Panacea Biotech Biological E Butantan Vabiotech	Chimeric infectious clones. Dengue-4 D-30 virus (non-structural) + dengue envelope & preM genes. Attenuated D30 dengue-4 virus	Tetravalent	Phase 1, adults
U.S. Centers for Disease Control and Prevention (CDC)	Inviragen	Chimeric infectious clones. Dengue-2 virus (nonstructural) + dengue envelope & preM genes	Tetravalent	Phase 1
Hawaii Biotech	Merck Vaccine	Recombinant envelope subunit	Monovalent	Phase 1

Table 1: Dengue Vaccine Candidates



Challenges, and opportunities to address the challenges

There are a number of significant challenges facing developers of dengue and other new vaccines. Some of the more important challenges are commitment of industrial partners, specific challenges faced by developing country producers, translational clinical research, establishing reliable demand projections and obtaining early purchase and delivery commitments.

1) Commitment of industrial partners.

Despite the involvement of several companies developing dengue vaccine candidates, there is always concern that some or all will drop out. Some of the companies could face technical or scientific challenges that limit either production capability or effectiveness of their products. Others may face internal competition with executives estimating that competing pipeline products could be more profitable. In the end, there is the possibility none of the current candidates may prove safe and

effective sending the entire field back to the research laboratories for further development.

Here, the public sector, including international organizations, has much to contribute. Product development partnerships (PDPs) in particular can play crucial roles by reducing risk and providing small-scale but critical funding.

2) Specific developing country manufacturing challenges.

Unlike other products that developing country manufacturers have focused on in the past, most dengue vaccine candidate products are relatively early in the development process. As a result, state-of-the-art laboratory, manufacturing and clinical development efforts will be required, not to mention clinical research and regulatory approval by national regulatory authorities. To succeed in the high-risk arena of vaccine

Dr. Mahoney is Director of Vaccine Access for the Pediatric Dengue Vaccine Initiative (PDVI), a program of the International Vaccine Institute (IVI), Seoul, Korea. In this role, he has responsibility for all activities to ensure access by the poor to the Dengue vaccines and diagnostics that PDVI helps develop, evaluate and introduce. From 1995 to 2002, he played a central role in the work to establish and launch the IVI where he was responsible for institutional development. He was also a co-founder of the International Task Force on Hepatitis B Immunization while with the Program for Appropriate Technology in Health (PATH). Before cofounding and joining PATH, he was a Program Officer in Population with the Ford Foundation.

development companies, depending on their previous experience, may require specific types of technical and financial assistance to navigate the various aspects of early stage development.

The public sector can help address these challenges. First, they can help offset vaccine development costs by bridging the translational research gap between basic research and clinical development. Here, progress can be accelerated by mobilizing expertise in areas such as clinical trial design, regulatory affairs and diagnostics¹⁵. Second, the public sector can assist in assuring that there is a large market, including tangible commitment from national policy makers and international partners to purchase safe and effective products¹⁶. Third, they can assist the companies in arranging for and financially supporting clinical trials. Fourth, they can assist companies in Brazil, India and Vietnam to construct state-of-the-art product development plans and production facilities that will increase the chance of meeting international standards and, therefore, being able to export to international markets¹⁷.

3) Establishing reliable demand projections. Vaccine producers need sound demand projections if they are to build facilities of appropriate scale and thus obtain production efficiency. The PDVI has completed a preliminary projection of dengue vaccine demand in selected developing countries¹. This study shows that potential

demand in the first five years following vaccine licensure could easily accumulate to more than 500 million doses. Further analysis of these projections is warranted to account for realistic likelihood of the pace of vaccine adoption by individual countries and the rate at which each country might introduce the vaccine.

4) Obtaining early purchase and delivery commitments. As solid safety, efficacy and cost data for dengue vaccines become available it will be important to mobilize funds and make purchase commitments to vaccine producers. The GAVI Alliance has taken a lead in this matter by formally considering the inclusion of dengue vaccine in its portfolio once a vaccine is licensed. PDVI will work with the GAVI Alliance, individual developing countries, WHO, and others through the Dengue Prevention Boards in Asia-Pacific and the Americas, to plan for procurement.

Clearly there is a need for a robust and innovative international financing mechanism that can support the investment decisions required of vaccine producers to put production facilities into place well in advance of actual product sales. One such mechanism that is being tested by the GAVI Alliance is advance market commitments (AMC)¹⁸. Others, such as a vaccine procurement baseline (VPB), have been proposed¹⁹. Regardless of what systems are eventually settled upon, concerted public effort is required on the part of donors to support the production and delivery of needed vaccines.

Resources needed

The types of resources necessary to bring viable vaccine candidates through production and to the market following successful clinical trials can be broken down as follows: financial, scientific and technical, human and logistical.

i) Financial resources. The cost to bring a new vaccine to market has risen dramatically in the past two decades, some have estimated by as much as 10 fold into the hundreds of millions of dollars²⁰. But there is a vast difference in the estimated costs of vaccine development depending on how many countries a company plans to market their product. Companies that plan to produce vaccines that address public and private markets in a wide variety of countries can be expected to incur greater costs in multiple-country trials and product registrations. In contrast, manufacturers, that plan to target only the public sector in a limited geographic area, may be able to complete high-standard development at considerably less expense¹³.

ii) Scientific and technical resources for vaccine manufacture. The intellectual property underlying the current set of dengue vaccine candidates comes largely from research institutes and public sources. The value of this property is an essential component that enables each company to mobilize funds to actually bring the vaccine through the expensive

development process²¹. There is also a great deal of valuable know-how that emerges as each company transforms their core technologies into actual products. Unlike the manufacture of drug compounds, which can be reproduced in generic manufacture, vaccines can never be produced as 'generic' products. This is because vaccines are complex biological products and not small-molecule chemicals⁸.

Technical resources available to the three multinational firms currently developing dengue vaccines are probably adequate to bring their vaccine candidates from their current state of development through large-scale manufacture and on to licensure assuming they demonstrate satisfactory safety and efficacy. This cannot be said of the developing country producers, few of whom have ever taken a vaccine all the way from early development to delivery. However, with the extensive experience in production of quality vaccines that all of these firms have already demonstrated, it is very likely that the remaining technical gaps can be filled by external technical assistance. With such assistance, the likelihood of success is considerably improved.

iii) Human and logistical resources. The ability to manufacture quality vaccines in significant quantities by each of the companies currently developing dengue

vaccines is well established although not all have achieved WHO prequalification. All have the human resources necessary for quality-controlled, high volume production and packaging of efficacious vaccines. However, it is likely that additional assistance will be required in that crucial stage where these new candidate

vaccines will have to be scale-up from pilot production of trial-size batches to full-scale manufacture. Fortunately, such assistance is available to those who may require it in the form of consultancies, recruitment of qualified individuals and experienced institutions that can be called upon to assist in areas of identified need.

Summary

If one or more of the current dengue vaccine candidates proves to be safe and effective, there will be an immense public health imperative to rapidly produce and deliver the vaccine to millions of at risk children and adults, many of whom will have few financial resources. An essential first step in ensuring adequate production capacity is the establishment of a global access strategy. That strategy must take into account all of the scientific, technical, intellectual property and resource needs of each of the companies that will produce the vaccine. To be successful, such a strategy must deliver innovative solutions to the obstacles that each manufacturer may face. Possibly the best hope for creating such a global approach will be through existing PDPs such as PDVI. PDVI and other PDPs have been established through the support of the Bill & Melinda Gates Foundation and other donors to address the universe of issues facing the introduction of new vaccines^{22, 23}.

In this review we have attempted to identify the capacities, weaknesses and needs of dengue vaccine producers both in the industrialized and developing countries. We have a great deal of confidence in the current set of producers from both the public and private sectors to complete and deliver adequate supplies of dengue vaccine should one or more of their products prove safe and effective. Particular challenges will be faced by developing country producers in scale-up and transition from laboratory-scale to full production of vaccines that meet or exceed all regulatory requirements. Resource needs will be considerable, and gaps that may need to be filled are expected, especially for post-licensure trials. Looking ahead, the technical and human resources needs of these companies will have to be carefully and realistically assessed and filled, sometimes with external sources of expertise, so as to achieve sustainable production of quality products.



References

1. Amarasinghe, A., et al., Forecasting dengue vaccine demand in disease endemic and non-endemic countries. *Human Vaccines*, 2010. In Press.
2. Mahoney, R., JE Maynard, The introduction of new vaccines into developing countries. *Vaccine*, 1999. 17(7-8): p. 646-52.
3. Hajjeh, R.A., et al., Supporting new vaccine introduction decisions: lessons learned from the Hib Initiative experience. *Vaccine*, 2010. 28(43): p. 7123-9.
4. CDC, Notice to readers: update on the use of pneumococcal conjugate vaccine in a setting of vaccine shortage - Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*, 2001. 50: p. 1140-42.
5. Bertrand, J., Vaccines: producers in countries of the Southern hemisphere *Med Trop (Mars)*, 2007. 67: p. 347-50.
6. GAVI. Facts and Figures. 2010 December 14, 2010]; Available: http://www.gavialliance.org/media_centre/facts/index.php.
7. Milstien, J.B. and M. Kaddar, The role of emerging manufacturers in access to innovative vaccines of public health importance. *Vaccine*, 2010. 28(9): p. 2115-2121.
8. Milstien, J.B., P. Gaule, and M. Kaddar, Access to vaccine technologies in developing countries: Brazil and India. *Vaccine*, 2007. 25(44): p. 7610-9.
9. Robbins, A. and I. Arita, The global capacity for manufacturing vaccines. Prospects for competition and collaboration among producers in the next decade. *Int J Technol Assess Health Care*, 1994. 10(1): p. 39-46.
10. Durbin, A.P. and S.S. Whitehead, Dengue vaccine candidates in development. *Curr Top Microbiol Immunol*, 2010. 338: p. 129-43.
11. Williams, K.L., et al., A mouse model for studying dengue virus pathogenesis and immune response. *Ann N Y Acad Sci*, 2009. 1171 Suppl 1: p. E12-23.
12. Beatty, M.E., G.W. Letson, and H.S. Margolis, Estimating the Global Burden of Dengue, in Second International Conference of Dengue and Dengue Haemorrhagic Fever. 2008: Phuket, Thailand.
13. Peny, J.M., O. Gleizes, and J.P. Covillard, Financial requirements of immunisation programmes in developing countries: a 2004-2014 perspective. *Vaccine*, 2005. 23(37): p. 4610-8.
14. Batson, A., Sustainable introduction of affordable new vaccines: the targeting strategy. *Vaccine*, 1998. 16 Suppl: p. S93-8.
15. Croft, S.L., Public-private partnership: from there to here. *Trans R Soc Trop Med Hyg*, 2005. 99 Suppl 1: p. S9-14.
16. Hanlin, R., J. Chataway, and J. Smith, Global health public-private partnerships: IAVI, partnerships and capacity building. *Afr J Med Med Sci*, 2007. 36 Suppl: p. 69-75.
17. Jadhav, S., et al., The Developing Countries Vaccine Manufacturers' Network (DCVMN) is a critical constituency to ensure access to vaccines in developing countries. *Vaccine*, 2008. 26(13): p. 1611-1615.
18. Schwalbe, N. and I. El-Ziq, GAVI's Advance Market Commitment. *Lancet*, 2010. 375(9715): p. 638-9.
19. Mahoney, R., S Ramachandran, ZY Xu, The introduction of new vaccines into developing countries II. Vaccine financing. *Vaccine*, 2000. 18(24): p. 2625-35.
20. Clemens JD and Jodar L, Introducing new vaccines into developing countries: obstacles, opportunities and complexities. *Nature Medicine* 2005. 11(S12 - S15).
21. Wilde, H., What are today's orphaned vaccines? *Clin Infect Dis*, 2001. 33(5): p. 648-50.
22. Mahoney, R., A Pablos-Mendez, S Ramachandran, The introduction of new vaccines into developing countries. III. The role of intellectual property. *Vaccine*, 2004. 22(5-6): p. 786-92.
23. Mahoney RT, et al., The introduction of new vaccines into developing countries. IV: Global Access Strategies. *Vaccine*, 2007 25(20): p. 4003-11

Occasional Papers are published by the Pediatric Dengue Vaccine Initiative of the International Vaccine Institute. They provide overviews of issues that are important for the development, introduction and delivery of dengue vaccines. The opinions expressed are those of the authors and do not necessarily represent the policies of the Pediatric Dengue Vaccine Initiative or the International Vaccine Institute.

This document is a publication of the International Vaccine Institute and all rights are reserved. Photocopying and distribution including through the internet for non-commercial purposes is permitted and encouraged providing all such copies include the following citation: An IVI publication, Seoul: International Vaccine Institute; 2010

As of 2011, the PDVI becomes the Dengue Vaccine Initiative Consortium which is comprised of the International Vaccine Institute, the International Vaccine Access Center of Johns Hopkins University, the Initiative for Vaccine Research of WHO, and the Sabin Vaccine Institute.

EDITOR:

Richard T Mahoney, PhD

rmahoney@pdvi.org

ASSISTANT EDITOR:

Kamonthip Wichmann

kwichmann@pdvi.org

