Key Messages:

- At least one dengue vaccine may be licensed by 2014.
- Currently dengue does not receive high priority by the global health community because of its low mortality.
- Dengue is associated with high morbidity and severe economic burden.
- Policy makers in dengue endemic developing countries accord very high priority to a dengue vaccine.
- Several new vaccines have recently been licensed and are placing additional financial burdens on procurement and supply systems.
- Dengue vaccination will have to include both catch-up and routine programs.
- PDVI has a “bottom up” strategy to support the efforts of endemic countries to plan for and implement dengue vaccine procurement and distribution.

Dengue Vaccine Adoption in Developing Countries: Some Cost and Financing Issues

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The development and introduction of dengue vaccines are particularly important. There are no effective drugs currently available for the treatment of dengue infection, and clinical care of dengue patients is impeded by both the lack of suitable diagnostics and the widespread lack of knowledge among clinicians concerning best practices for management of dengue patients. Further, vector control campaigns have to date proven to be neither highly effective nor sustainable. Thus dengue vaccines will be essential for the eventual control of dengue in developing countries. There are a number of dengue vaccines under development that could begin entering widespread use in the not-too-distant future.
Some implications for the introduction of dengue vaccines

An issue that will increase costs of dengue vaccine introduction will be the need for catch-up immunization of children and young adults, and perhaps, even adults in the early years of vaccine availability. In the Americas the highest incidences of dengue infection and morbidity are seen in individuals 10 years and older; shifts to older age groups are also becoming increasingly evident in Asia. Another potentially complicating issue is the product profile. For example, the sanofi pasteur vaccine candidate (a yellow fever-dengue chimeric vaccine) is being administered in clinical trials in a three-dose schedule of 0, 6 and 12 months, beginning at 12 months of age. This suggests that special immunization programs will have to be established for this vaccine alone. On the other hand, it is possible that a National Institutes of Health vaccine candidate (a combination of chimeric vaccines with gene deletions) might be effective when given as a single dose from 12 months of age. Such a vaccine would greatly simplify immunization strategies and would significantly reduce associated costs.

Introduction

At this time the price of these vaccines is not known and because of the uncertainties with respect to the regulatory process, scale-up of production, volume of uptake in the marketplace, and a number of other unknowns, it is not possible to make precise calculations of possible prices for dengue vaccines. Nevertheless it is possible to make some observations about the cost implications of adoption of new dengue vaccines.
Nevertheless immunization of older children and young adults would still be required and delivery mechanisms would need to be created or strengthened to reach these populations, using approaches such as school-based programs, immunization campaigns, and clinic-based programs. Finally, logistical challenges in the cold chain and storage systems will need to be addressed as they will for other new vaccines.

Another challenge facing the adoption of dengue vaccines is the fact that the disease occurs almost exclusively in developing countries. Unlike other new vaccines such as human papillomavirus (HPV), rotavirus, and pneumococcal conjugate vaccines, there will only be relatively small markets for dengue vaccines in developed countries. There will be the potential for purchases by travelers going to endemic countries and purchases by the military of various countries sending troops to or with troops in dengue endemic areas. However it is very difficult to estimate the size of these markets. Regardless, it is clear that vaccine manufacturers could not earn the same high profits in developed countries from dengue vaccines as with the other new vaccines.

Thus an assessment of the impact of financial factors on the procurement and distribution of dengue vaccines should include an option where no significant developed country markets exist.

Yet another issue affecting the availability of resources to procure and distribute dengue vaccines is the relatively low priority accorded to dengue by the global health community. Since the early 1990s, the global health community has assigned highest priority to human immunodeficiency virus (HIV), TB, and malaria vaccines. In recent years more attention has been paid to diarrheal disease vaccines and respiratory disease vaccines but dengue still remains largely a low priority vaccine among the global health community. On the other hand, concerns about dengue among health officials in endemic countries are considerable and may even be increasing. A study conducted by DeRoeck and others provided evidence that policy makers in Southeast Asia would give high priority to the introduction of dengue vaccines in endemic countries in the region. These studies have recently been repeated and expanded by Don Douglas and Denise DeRoeck of PDVI, and the studies confirm a very high priority for dengue vaccines among endemic country policy makers (unpublished data).
Dengue is a high priority in endemic countries because of a few unique features of the disease. First, it appears in epidemics and the epidemics can be huge. When an epidemic begins, the general population, parents in particular, become frightened at what they perceive to be the high likelihood that their children will be infected. Second, and as noted above, there are no available drugs for treatment of dengue once a child is infected and not every physician is aware of or familiar with the best practices for management of patients with dengue. Finally, dengue has become a ‘political’ disease because health officials have few effective tools at their disposal with which to quickly control the epidemic; vector control responses are often haphazard and ineffective. Thus health officials see dengue as not only a disease that can cause illness and death among the population but can also lead to the loss of their own jobs.

An important factor affecting the potential capacity to purchase and distribute dengue vaccines is the welcome influx of a number of new vaccines, such as HPV, Japanese encephalitis, rotavirus, and pneumococcal conjugate vaccines, that have the potential to prevent enormous burdens of the respective diseases in developing countries. However, their near-contemporaneous introduction has placed extraordinary financial burdens on international donors and national budgets. Some countries such as Thailand have declined to adopt and distribute the rotavirus and HPV vaccines for the time being, primarily because of the costs involved. It is possible that, since the diseases targeted by these recent new vaccines are a high priority to the global health community, substantial efforts to find new and creative sources of funding for procurement will be explored and assessed. The attempt to use Advanced Market Commitments (AMC) for the procurement of pneumococcal conjugate vaccines is a
good example. It remains to be seen whether additional novel global efforts will emerge to find new and innovative mechanisms of vaccine procurement for the introduction of dengue vaccines in endemic countries. However, another possible scenario is that the developing countries themselves will lead the effort to procure and introduce dengue vaccines. It is quite likely that there could be several ‘early adopter’ countries, lower- to middle-income countries as categorized by the World Bank, who see dengue as of sufficient public health and political priority that they would mobilize funds from their own national resources for the procurement of the vaccine. Such early adopter countries could include Brazil, Cuba, Indonesia, Thailand, Vietnam, and the Philippines.

This sequence of events would mimic what happened in the case of hepatitis B vaccine. Throughout the 1980s and most of the 1990s hepatitis B was not a high priority among the global health community; indeed some in the global health community resisted efforts to introduce the vaccine. A number of early adopter developing countries such as Indonesia and Thailand proceeded with their own resources.

As more countries became interested in introducing and expanding the use of hepatitis B vaccine they put pressure on officials of the World Health Organization and other international agencies to help them with their efforts. Eventually, with the advent of GAVI Alliance and funding from the Bill & Melinda Gates Foundation, the international community raised the priority for hepatitis B vaccination substantially and launched major efforts to help developing countries introduce the vaccine.

The Pediatric Dengue Vaccine Initiative (PDVI) has developed a ‘bottom-up’ strategy for planning for mobilization of resources for procurement and distribution of dengue vaccines. This strategy involves working with and among lower- and middle-income endemic countries to help them plan well in advance for the introduction and use of dengue vaccines. This work includes:

(i) helping national regulatory authorities to be able to provide high quality review of applications for clinical trials and for licensure,
(ii) developing field sites for collection of epidemiological and surveillance data that can help health officials to understand the burden of disease in their country,
(iii) establishing field sites for the clinical evaluation of new vaccines to help national officials understand how the vaccines perform in their country,
Developing country manufactures can play a particularly important role in supplying low cost, high quality vaccines. A recent successful example in this area is the work by PATH on Japanese encephalitis vaccine with a Chinese manufacturer, which led to the availability of a low price, high quality vaccine for use in countries with a per capita gross national product of less than US$1,000 until at least the year 2025\(^5\). With respect to dengue, PDVI is working closely with the Butantan Institute in Sao Paulo, Brazil. The Institute is committed to supplying a vaccine that will be priced at a level to ensure affordability by developing countries. As with HPV vaccines\(^1\), countries will need to consider a number of delivery strategies especially for catch-up immunization in the early years of dengue immunization. These could include school-based programs, vaccination during established health days or other community outreach activities and campaigns to reach young people. For dengue, private clinics could play a particularly important role given the high priority that a number of older individuals would assign to obtain dengue vaccination. Individuals even in their 20s and 30s may wish to receive dengue immunization; some of these individuals would have the capacity to cover the costs of the vaccination. For example, a study in the Philippines showed a very high level of willingness to pay (mean willingness to pay ranged from US$27 to US$32) for a dengue vaccine\(^6\). The willingness of international and national health policymakers to accord high priority to the purchase, introduction and distribution of dengue vaccines will depend on a number of other factors not discussed in detail here. These include detailed cost-effectiveness analyses and detailed and accurate burden of disease assessments.

PDVI works (cont.)
(iv) working with developing country manufacturers (e.g. in Brazil and India) to help ensure adequate supplies in early adopter countries,
(v) conducting policymaker studies so that the international community and policymakers themselves may reflect upon and understand the policy issues that would be most important to resolve for effective introduction of dengue vaccines, and
(vi) convening two Dengue Prevention Boards (one in the Americas and one in the Asia-Pacific region) involving experts from several potential early adopter countries who can be focal points for the provision of needed and accurate information about various aspects concerning the introduction and deployment of dengue vaccines.
Crucial, of course, will be the actual prices that manufacturers offer once the vaccines are licensed. These prices will be greatly influenced by the size of the markets, by the presence of competition, and by the ability of procurement agencies to negotiate effectively to obtain low prices. One factor that may help in these negotiations is a detailed knowledge of the cost of production of dengue vaccines. To assist in this way, the PDVI is undertaking a detailed cost of production study, the results of which should be available before mid-2011.

Conclusion

It is widely recognized that perhaps the greatest challenge to the introduction and distribution of new vaccines in developing countries is the substantial financial demands which these activities place upon international donors and national governments. A number of new vaccines have recently entered the marketplace and are competing for scarce resources so that they can be introduced into national immunization programs. The licensing of one or more new dengue vaccines could occur as early as 2013 or 2014; the initial price of these vaccines is unknown but it is likely that initially at least they will be on the order of several dollars per dose. This level of pricing will mean that developing countries and international donors will be faced with difficult challenges to raise the required financial resources. However with expanding markets, with competition, and with clear understanding of the importance and severity of dengue infection in the health and well-being of people in many developing countries, one can be optimistic that there will eventually be wide scale use of dengue vaccines to control this important disease in many endemic countries.
References


