Key Messages:

- Many new vaccines are under development or are available for introduction.
- The introduction of a new vaccines requires sound supportive data particularly of cost effectiveness.
- WHO has prepared excellent guidelines to be employed by developing countries to guide vaccine introduction.
- The introduction of dengue vaccines will require good cost effectiveness data based on sound surveillance systems employing high quality diagnostics.
- As recommended by the Dengue Prevention Boards, there is a need to develop improved dengue diagnostics particularly for the first few days following onset of fever.
- There is also a need to improve dengue surveillance in endemic countries based on Dengue Prevention Board recommendations and WHO guidelines.
- There are inadequate data on the burden of dengue and more studies are required. Dengue is spreading rapidly and older studies are clearly underestimates of the true level.
- There need to be additional and more accurate measurements of the economic costs of dengue. A number of studies indicate that past estimates greatly underestimated the costs.

An Overview of Challenges concerning Diagnosis, Surveillance, Burden of Disease, and Economics of Dengue

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The purpose of this occasional paper is to outline the complex challenges facing the laboratory diagnosis and surveillance of dengue, which in turn raise challenges facing efforts to estimate the burden and costs of the disease, and how these multiple challenges might affect the development, registration and eventual introduction of dengue vaccines.

The burden of the diseases targeted by new vaccines is often greatest in those populations and countries least able to afford them (e.g. rotavirus and pneumococcal infections, and disease resulting from human papillomavirus (HPV) infections).

One approach to this apparent impasse has been to ‘transfer’ bulk materials, technologies and expertise from institutions and companies in industrialized countries to vaccine manufacturers in developing countries.
Besides technology transfer, another approach has been a variety of innovative funding mechanisms, under the auspices of agencies such as the Pan American Health Organization and the GAVI Alliance, which have been effective in getting vaccines to some of those most in need\(^1,2\).

However, these strategies have their limitations: most of the technologies required to produce new vaccines have not yet been developed by vaccine manufacturers in developing countries and there are many countries needing assistance from, for example, the GAVI Alliance, to purchase ‘traditional’ National Immunization Program (NIP) vaccines let alone ‘available but underutilized’\(^3\) vaccines.

Indeed, a recent review of aspects of the GAVI Alliance immunization funding strategy stated that “funding gaps will remain and financial sustainability would be far from assured in most cases”\(^4\).

Moreover, there is a myriad of underutilized vaccines and future vaccines-in-development, the so-called vaccine ‘pipeline’\(^3\). Even without including Haemophilus influenzae type b (Hib) and hepatitis B vaccines, the underutilized vaccines include cholera, HPV, Japanese encephalitis, pneumococcal conjugate, rabies, rotavirus, rubella, typhoid and yellow fever vaccines, and the future vaccines include the “imminent”\(^5\) meningococcal serogroup A conjugate vaccine, HIV/AIDS, malaria and tuberculosis vaccines, as well as a dengue vaccine\(^3\). Therefore countries have to prioritize which new vaccine(s) to introduce based upon several factors, including (i) the burden of the particular disease, (ii) the affordability of the particular vaccine, and (iii) the capacity to introduce that vaccine into the NIP.

The World Health Organization (WHO) has provided guidance on the general
principles involved when considering the introduction of a new vaccine into a NIP. These principles define two sets of key issues to be considered: policy and programmatic issues. The policy issues are further separated into (i) public health priority, (ii) disease burden, (iii) vaccine efficacy, quality and safety, (iv) other interventions including other vaccines, and (v) economic and financial considerations.

Dengue has some key features when considering the first two of these issues: it causes periodic epidemics, which can be of an extraordinary magnitude, but between epidemics it may be a very low public health priority, and although it causes high morbidity it has a relatively low mortality. Indeed, it would seem that dengue vaccines are at a disadvantage in the way they have been positioned in the pipeline if mortality is used as a dominant indicator. What is known and what needs to be known about the public health priority of dengue in endemic countries to justify the (eventual) introduction of a dengue vaccine into a NIP?

Central to the economic and financial considerations are cost-effectiveness analyses, to assist in deciding “whether investment in a new vaccine achieves greater or lesser health outcomes relative to investment in another type of vaccine presentation or public health programme.” WHO has subsequently provided even more detailed guidance on how to evaluate the cost-effectiveness of vaccines. Clearly this is a complex and resource intensive process; it requires epidemiological, disease burden and costing data (some of which will either not be available or of poor quality in some developing countries) and expertise in economic modeling with a capacity to make evidence-based policy decisions (which again may not be available in some developing countries).
Future dengue vaccines are moving through the vaccine pipeline\(^5\), and Phase 2 clinical trials have commenced with at least two dengue vaccine candidates\(^8\). Even though the product ‘profile’ of a licensed dengue vaccine is unknown at this time, dengue vaccines will need to be tetravalent (i.e. capable of protecting against all four serotypes), they will probably require multiple doses and some will require sophisticated production and manufacturing technologies. Therefore, it is likely that dengue vaccines will be, initially at least, considerably more expensive than the traditional NIP vaccines. Furthermore, a dengue vaccine will probably need to be given routinely in endemic countries in the second year of life, at an age not included in many current NIPs.

In other words, there could well be extra scaling-up costs to the program, above and beyond those required for the purchase and administration of the vaccine.

Therefore endemic countries will need to consider the cost-effectiveness of future dengue vaccines, using the procedures detailed in the WHO guidelines\(^7\). This will require (i) costs and other economic data as inputs into the models used, and also (ii) burden of disease data. This in turn will require (iii) epidemiological data derived from disease surveillance, which in turn will require (iv) laboratory diagnostic capacities.

Each of these requirements poses challenges that must be met if endemic countries are to make decisions about the priority to give to introducing and funding dengue vaccines. The Pediatric Dengue Vaccine Initiative (PDVI) recognizes these challenges, and has made efforts to address them in a systematic way.
Challenge 1: The need for improved dengue diagnostic tests

Accurate disease surveillance requires concise and applicable case definitions for the ascertainment of the diseases under surveillance. Case definitions usually consist of a constellation of defined clinical signs, and may also require some laboratory indicators as well. Dengue has no pathognomonic clinical features; indeed, there are no features that reliably distinguish dengue, especially early in the illness, from several other acute febrile illnesses that also occur in dengue endemic countries, and therefore laboratory tests are required to confirm the diagnosis. Recognizing the importance of reliable diagnostic tests, PDVI supported a recent evaluation of several commercially available dengue IgM detection kits; while this evaluation revealed that some kits performed poorly, those that performed adequately are to be included in the WHO Bulk Procurement Scheme.

PDVI has also convened two regional (Asia-Pacific and The Americas) Dengue Prevention Boards, with members and advisors who have considerable expertise in various aspects of dengue. At meetings to discuss dengue diagnostics, Board members identified several practical barriers concerning the effective use of dengue diagnostic tests: (i) test kits may not be available, (ii) patients may not be able to afford the costs of the tests, (iii) patients may not be prepared to return to a health facility to provide a convalescent serum sample, (iv) some clinicians may believe that they are so familiar with dengue that there is no need for a test, (v) some clinicians may not request tests because the results are not available in time to inform the management of the patients, and (vi) some clinicians may not have confidence in the tests, because of a poor understanding of the timing of viremia and the antibody responses to dengue virus infection, and the capabilities of the various tests. The Board members emphasized the need for an accurate, rapid and affordable diagnostic test that covers the early days of disease, and can be used at the point of care, even in peripheral and remote settings, on a single acute sample.
Challenge 2: The need for more effective surveillance of dengue

Good surveillance of dengue is essential for several reasons: it should be used for the timely targeting of vector control activities, it should be used to describe the epidemiology of the disease over time (and could therefore be used to assess its costs) and it should be used to evaluate the effectiveness of interventions such as vector control and eventually, dengue vaccines. However, the reality is that in many countries dengue surveillance is either incomplete or of poor quality (or both). For example, in some countries only hospitalized cases are notified whereas in others only pediatric cases are notified. In some countries only a small portion of the cases are confirmed by laboratory tests, and very few countries implement ongoing virological surveillance of the prevalent serotypes.

The Dengue Prevention Boards have also met to discuss surveillance strategies and to suggest best-practices for dengue surveillance. The Board members emphasized the importance of obtaining accurate surveillance data, as they are needed to assist policy makers at all levels to give dengue an appropriate level of priority in the allocation of resources. The Board members recommended that high priority be given to improving dengue surveillance in endemic countries and those that report frequent outbreaks, and recommended that dengue be a notifiable disease in legislation in affected countries, that laboratory confirmation should be sought on all ‘dengue-like’ or ‘suspected dengue’ cases except during epidemics when only a sample need be tested, that regional WHO case definitions should be used, that data should be analyzed so as to provide incidence rates of dengue, DHF and DSS as well as hospitalization and mortality rates, and that efforts be made to reduce any reporting delays. The Board members also considered that it was important to
evaluate the dengue surveillance system, so as to determine the quality of the data, using, for example, periodic active sentinel site surveys. Virological surveillance was also considered to be essential, so that trends in serotypes (and genotypes) can be tracked and correlated with disease patterns over time.

PDVI has also formed a consortium of field sites in Asia and the Americas; these sites have been selected with the intended purpose that they ultimately serve as potential sites for clinical trials of dengue vaccine candidates. As part of their core activities, the sites either implement existing or develop competent laboratory-based disease surveillance, and hence are in effect sentinel sites for dengue surveillance. Efforts are made to harmonize the surveillance and laboratory procedures, and the data management processes used in the sites. The surveillance data obtained from each field site could therefore be compared with the respective country’s reported surveillance data for the same region (as the site), and from this comparison ‘expansion factors’ could be calculated. These factors could then be applied to data obtained from national surveillance systems to obtain more accurate incidence data.
Increase of dengue shown in Figure 1 has been attributed to several major determinants, particularly urbanization (much of it unplanned, and without parallel expansion of basic infrastructure) and international travel\textsuperscript{14}. Both of these determinants have grown at an unprecedented pace over these decades; a consequence of the latter, in particular, has been the increase in the number of countries that have reported local transmission, indeed in some cases endemic transmission, of dengue.

However, as already discussed, surveillance for dengue remains quite inadequate in many developing countries that have endemic transmission and therefore the numbers of cases reported to WHO markedly underestimate the actual incidence of dengue.
As a consequence any attempt to estimate the magnitude of its impact on human health will have to deal with considerable uncertainties.\textsuperscript{15}

Acknowledging these uncertainties, PDVI has undertaken a preliminary reappraisal of the global burden of dengue\textsuperscript{16}; previous estimates were made over 10 years ago\textsuperscript{17}, and clearly the global burden has increased considerably since then. An updated estimate of the population at risk for dengue has been derived from available census data, and by applying incidence data from cohort studies, estimates of symptomatic dengue infections and DHF have been derived. Then by assuming an overall DHF case fatality of 1\%, the estimated annual number of deaths has been calculated. These preliminary estimates indicate that about 55\% of the world’s population live in countries where dengue transmission occurs, and that there may be as many as 36 million cases of dengue annually, with 2 million cases of DHF and 21,000 deaths.\textsuperscript{16} Apart from mortality, which has remained unchanged, these estimates are several-fold greater than those described previously; further refinement of these estimates is in progress.
Even without consideration of the shortfalls of reliable incidence or burden of disease data, estimating the economic costs of dengue is intrinsically difficult. For example, when examining the cost of illness, how is information on those managed as outpatients to be obtained? How is information on those managed by private practitioners to be obtained? If indirect costs are to be included, how are they to be obtained? When examining the societal burden of disease, what disability score should be used to calculate disability-adjusted life years (DALYs)? What about the costs of routine vector-control programs? How are the extra costs involved in an outbreak or epidemic going to be considered?

PDVI has recently undertaken a literature review of publications pertaining to the economics of dengue. Although the review revealed a dearth of such publications, with few of relevance to the topic, several conclusions can be made.

First, the burden of dengue, calculated as DALYs is substantial. Among Thai school children for example, the mean burden of dengue was 465 DALYs per million per year. Second, the costs of outpatient management of cases, and the indirect costs are substantial accounting, in Thailand, for 44-73% of the DALYs lost to dengue each year. Third, reflecting the concerns of parents and other caregivers, the costs of dengue at the household level can be considerable. Indeed, in Cambodia the "costs were often catastrophic", causing some families to sell assets and incur long-term debt.

The PDVI systematic review also assessed that the most recent WHO estimates place the global burden of dengue at 104 DALYs/million population or 670,000 million DALYs annually. For these estimates dengue fever was assigned a disability score of 0.2 and duration of 5.5 days, and dengue hemorrhagic fever was assigned a disability score of 0.5 for 11 days.
In the same report an uncomplicated febrile episode of malaria was assigned a disability score of 0.4721. However, the systematic review noted that seven of the eight publications by non-WHO researchers used a disability score of 0.81 or higher for both dengue fever and dengue hemorrhagic fever. Further, a recent study from Malaysia reported that the quality of life was significantly impaired for 9 days in non-hospitalized dengue patients and for 13 days in hospitalized dengue patients. Therefore, these recent studies indicate that the dengue disability scores and duration used for making the WHO estimates were probably too low; indeed, using the higher disability scores proposed by Gubler and Meltzer would likely increase the global DALY estimates by 3-4 fold.

PDVI has begun to improve this situation by supporting research to provide further information on the true burden of dengue. This includes a recently published eight-country study that reported that the mean cost of illness of dengue in these countries was I$514 (I$ = International Dollars) and I$1,394 for ambulatory cases and hospitalized cases, respectively. Other PDVI-supported research into the economics of dengue has been described in several additional publications.

Because the economic costs of dengue will be crucial for the necessary cost-effectiveness analyses of dengue vaccines, PDVI has convened an expert panel to consider research priorities in an effort to address some of the information gaps. A detailed report on these priorities is in preparation; however, the experts did emphasize the need for a standardized approach, and recommended that when undertaking economic and cost-effectiveness analyses, the recent WHO guidelines on the economic evaluations of immunization programmes be utilized and adhered to.

**Conclusion**

There are clearly numerous ‘up-stream’ challenges that need to be addressed before dengue vaccines can be funded and widely used in NIPs. PDVI is endeavoring to meet some of these challenges through its various program areas, and has supported a variety of projects and studies that have already begun to provide some of the necessary (and more contemporary) information.
References


References (cont.)


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