From the Editor’s Desk

This Occasional Paper is an essay by Dr. Jeffrey Hanna considering the issues to be addressed in introducing a dengue vaccine into a national immunization program. The essay is forward looking – a dengue vaccine may be licensed within the next few years. We believe that such a forward view is timely because there is ample evidence that it can takes years if not decades for immunization programs to introduce new vaccines. It is not too early to start planning for dengue. As the date of licensure of a dengue vaccine approaches, various groups at the global (e.g. SAGE), regional (e.g. WHO regional offices) and national levels will start to tackle the complex issues surrounding introduction of dengue vaccines. Dr. Hanna’s essay provides us with his views of the multitude of issues to be addressed and, in some cases, how he feels they might be resolved.

This Occasional Paper has an additional importance beyond identifying dengue vaccine introduction issues. It clearly shows that the introduction of a dengue vaccine will require expertise not only at the national level but from a variety of other agencies such as WHO and those with in depth technical knowledge of the vaccine. The PDVI and its collaborators represent a unique international repository of much of this technical knowledge, and PDVI will work closely with national immunization programs to facilitate effective introduction and delivery of dengue vaccines.

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

Dengue Vaccines: Introduction and Delivery Issues

Jeffrey N. Hanna

The development of a new vaccine, its progression through the various clinical studies and trials to registration, along with the industrial scale-up of production can take many years, and because these processes are permeated by uncertainty and unpredictability, they represent a high-risk intellectual and financial investment. However, once a vaccine is registered, and it is available for bulk supply, and funding has been obtained for it to be utilized, there are still risks and challenges to be overcome. Indeed, this is now the time for the public health community, with the assistance of those with expertise in communications, immunization program management and several other disciplines to ensure that the new vaccine can be introduced into existing programs as seamlessly as possible, that uptake of the vaccine increases according to expectations and that high coverage, once achieved, is sustained.
The World Health Organization (WHO) has provided guidance on the general principles involved when considering the introduction of a new vaccine into a National Immunization Program (NIP), and on various practical issues that need to be addressed when implementing the decision to introduce a new vaccine\(^1\). This paper has drawn extensively from the WHO guidelines and from the author’s considerable experience gained from introducing new vaccines into the Australian NIP.

It must be recognized from the outset that introducing a dengue vaccine will be particularly challenging. It will have a complex vaccination schedule, and will probably have to be given from the second year of life, at a time when few other vaccines are given routinely. Catch-up vaccination of older age groups will probably be necessary.

This paper details these and some other complexities that will have to be considered when introducing a dengue vaccine, but as there is not (yet) a registered dengue vaccine, this overview must be considered as preliminary and tentative. Details relevant to the introduction of dengue vaccines will be clarified and become more specific as the vaccine candidates are further developed, so that more definitive recommendations can eventually be made.
Formulating a national policy for a dengue vaccine

Ideally, every country should have a National Immunization Committee (NIC) consisting not just of pediatricians and public health physicians, but also representatives of other relevant medical specialties and of those involved in delivering vaccines, e.g. family physicians, community health nurses, and health workers. In many industrialized countries, a consumer representative is also included on the NIC.

The NIC has various responsibilities, one of which is to determine national policies for new vaccines. In order to do this, the NIC should examine the available epidemiological information about the relevant disease. In the case of dengue this includes the dengue fever incidence and age distribution, the dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) incidence and age distribution, seroprevalence data, serotype trends over time, etc. The NIC might have to recommend further surveillance or commission research to obtain any essential data that are lacking.

The NIC should also examine what is known about the vaccine from pre-registration studies, and from experiences in using the vaccine in other countries: safety, immunogenicity, efficacy, effectiveness, etc. The NIC would also need to review any cost-effectiveness studies undertaken in similar situations elsewhere.

The ‘product profile’ of the vaccine should also be considered and several questions addressed:

a) What is the vaccine ‘presentation’? Are there vials or pre-filled syringes? Is it a mono- or multi-dose presentation? Is it a liquid vaccine or does it require reconstitution?

b) How was the vaccine prepared? Has the vaccine virus been cultured, passaged or produced in any way that could generate community concerns that would need to be managed? For example, is it a ‘genetically modified’ virus? Would a virus passaged in primary dog kidney (PDK) cell cultures be acceptable to all populations?

c) What additives are included in the vaccine? Are there adjuvants that might contribute to adverse events following immunization (AEFI)? Are there preservatives that could generate community concerns? Does the vaccine contain antibiotics or stabilizers?
d) What age ‘parameters’ around the vaccine have been set by the registration? What is the recommended primary dengue vaccination schedule for young children? What are the recommended schedules for catch-up vaccination of older individuals? Have lower and upper age limits been defined for the vaccine?

For the purposes of this paper on the introduction of a dengue vaccine, it is assumed that:

i) Either an inactivated, adjuvanted vaccine or a live, attenuated vaccine would be registered for use in country programs

ii) The vaccine would be registered for use from 12 months of age, with no upper age limit

iii) The vaccine would require a multidose schedule. It is assumed that for primary immunization, three doses spaced over at least six months are required

iv) The vaccine would be administered by the subcutaneous (SC) route, and

v) The vaccine would require transport and storage at the recommended cold chain temperatures (usually between +2°C and +8°C).

From the above considerations, and considering the logistics and requirements of the existing NIP, the NIC should develop national policies about the use of the selected dengue vaccine. The policies should be as evidence-based as possible, depending upon the available epidemiological information about dengue and the expertise of the NIC members. These policies would have costing and funding implications, or once finalized could be used as critical information to support approaches to potential funding sources.

For the purposes of this paper, it is assumed that funding would be available to purchase the dengue vaccine (so that it would be available free when provided through the NIP), and that it would be available in bulk for use in country programs. (It is well recognized that the former assumption is particularly optimistic, but it allows for an examination of the most comprehensive requirements for the introduction of the vaccine).
Dengue vaccine recommendations

Vaccine management and cold chain: The NIC must ensure that dengue vaccine is transported, handled and stored in accordance with existing NIP policies, protocols and procedures, including vaccine ordering, stock rotation and inventories. There needs to be adequate infrastructure to be able to cope with the vaccine’s transport internationally, nationally, regionally and locally, ensuring that vaccine management during ‘outreach’ clinics is included.

There must be adequate cold chain capacity to cope with the extra demands of the dengue vaccine added on to those vaccines already in the NIP. Is there a diluent that also needs to be managed within the cold chain? Is there adequate capacity centrally/locally? Is the cold chain being correctly managed and monitored, particularly in rural and remote clinics? Are any incorporated vaccine vial monitors (VVMs) being used as recommended by WHO? What should be done with dengue vaccine that has been inadvertently stored at >0°C to 1°C? at ≤0°C? at ≥9°C? Is provision made for the extra precautions that need to be in place for seasonal events, such as cyclones, hurricanes and floods?

The NIP also has to ensure adequate supplies of the other consumables that may be required for dengue vaccination: syringes, needles, waste disposal receptacles, etc.

Vaccination schedule: The recommended schedules for each age group should be stated by the NIC very clearly with no opportunity for ambiguity. It would be preferable to have specific ages, rather than age ranges (i.e. the age for the first dose should be recommended as, for example, 12 months of age, rather than 12 to 15 months of age).

For example, the primary dengue vaccination schedule recommended by the NIC might be: 12, 14 and 18 months of age. The NIC would then need to consider what to recommend if the vaccine is inadvertently administered to a child <12 months of age (i.e. younger than the lower age limit defined by the vaccine’s registration and younger than the NIC recommendation). There would need to be a recommendation as to whether this dose would be considered as ‘invalid’, and a replacement ‘valid’ dose offered as soon as is practicable.

The NIC should also make recommendations about the acceptable minimum intervals between doses, and what remedial actions need to be taken if doses are given earlier than these minimum intervals. Similarly, recommendations should
be made if the second or third doses are given later than the recommended timing. The usual recommendation given in this situation is that there is no need to repeat the late vaccination or to restart the vaccination schedule, but rather to accept those that have been given, although belated, as valid. If the second dose was given late, the third dose could be ‘accelerated’ and administered according to the recommended minimum interval.

The NIC should also recommend ‘catch-up’ dengue vaccination schedules for older individuals. This would be necessary even if there were no funding for a catch-up component to the dengue vaccination program, because the vaccine may well be used for catch-up in the private sector. The number of doses of a vaccine required for older individuals may be fewer than those required for younger children as is, for example, recommended for the bacterial conjugate vaccines. The reasons include more robust immune responses and possible naturally-induced immunity in older individuals. This may also be the case for dengue vaccines, but for the purposes of this overview, it is assumed that:

i) A three-dose schedule, of 0, 2 months (i.e. two months after the first dose) and 6 months (i.e. six months after the first dose, or four months after the second dose) is required for older individuals, and

ii) Funding is available for a catch-up program for individuals up to 14 years of age (i.e. up to the day before the 15th birthday). (NB: The epidemiology of the disease in any country could have considerable influence upon the upper age limits of a catch-up program.)

Again, minimum intervals would need to be recommended, and recommendations given about the management of doses that are given too early. Similarly, recommendations would need to be made on the management of doses that are given late. So as to prevent ‘leakage’ of funded vaccine to older people, it would be particularly important to emphasize the upper age limit of the funded program, and that those 15 years of age and over are not eligible for free dengue vaccination. An exception could be made for those who have already received one or two doses of (free) dengue vaccine before the 15th birthday, so as to encourage their completion of the vaccination schedule even though they have turned 15 years of age.
It would be important that the NIC state clearly the date when the funded catch-up program is to finish; after this time the only routine funded vaccination is that of young children from 12 months of age.

**Contraindications to dengue vaccination:** As with all vaccines, dengue vaccines would be contraindicated if:

i) There is a known anaphylactic sensitivity to any vaccine component, or

ii) There has been documented anaphylaxis following a previous dose of the same dengue vaccine.

The NIC would need to consider further specific contraindications for the live, attenuated dengue vaccine. For example, the following two contraindications are based upon those that apply to other live, attenuated vaccines:

**i) Severe immunosuppression through either disease or treatment:**

The live, attenuated dengue vaccine should not be administered to persons with acquired immunodeficiency syndrome (AIDS), or to persons known to be infected with the human immunodeficiency virus (HIV), unless the latter do not have severely impaired immunity (i.e. have a CD4+ lymphocyte count of >15%)².

The significantly immunosuppressive dose of oral steroids is ≥2 weeks of daily ≥20 mg or ≥2 mg/kg body weight of prednisone (or equivalent)⁶. Persons who were on this dose could be given the live, attenuated dengue vaccine after the steroid therapy has been discontinued for at least one month.

NB: Although the inactivated, adjuvanted dengue vaccine could be given safely to severely immunosuppressed persons, the immune response is likely to be suboptimal, and therefore should only be used in this situation if there is no other alternative.

**ii) Pregnancy:**

It does not appear that dengue infection in pregnancy leads to adverse outcomes⁷. In particular, the dengue virus is not known to be teratogenic; there is no known ‘fetal dengue syndrome’. Furthermore, the live, attenuated yellow fever vaccine has been (inadvertently) given to large numbers of pregnant women with no evidence of adverse outcomes⁸. Nevertheless, for theoretical reasons at least, the live, attenuated dengue vaccine should not be administered to pregnant women, particularly during the first trimester. However, women inadvertently vaccinated in early pregnancy could be reassured that there is no known evidence of risk to the pregnancy; there would not be grounds for a termination of pregnancy.
**Precautions to dengue vaccination:** Precautions are conditions that may either predispose a person to a severe AEFI, or lead to a suboptimal immune response following vaccination. Provided that the person could be guaranteed to return, vaccination could be postponed until after the precaution is no longer applicable, but the NIC should emphasize that if there are limited opportunities for vaccination (e.g. in remote areas serviced by outreach clinics) the precaution(s) should be ignored, and the opportunity used to vaccinate the person. Similarly, if the person to be vaccinated could not be guaranteed to return, the precautions should also be ignored.

A precaution to either dengue vaccine is an intercurrent illness, with or without a fever, of at least moderate severity. The rationale for this is to avoid any confusion between the manifestations of the illness and vaccine adverse events, and to avoid any possible allegations that the vaccination ‘worsened’ the illness. NB: Persons with mild illnesses should be vaccinated (see below).

The NIC would need to consider further specific precautions for the live, attenuated dengue vaccine.

For example, the following precautions are based upon those that apply to other live, attenuated vaccines:

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i) **Receipt of another live vaccine, including measles-containing, varicella, yellow fever vaccines and the live, attenuated Japanese encephalitis vaccine, within the previous four weeks:**

This is because there is some evidence, albeit limited, of interference between the immune response from the first live vaccine and that of a second live vaccine given within four weeks of the first. Live vaccines can be given simultaneously (but in separate syringes, at separate sites), but otherwise should be separated by four weeks. [NB: this does not include the live oral poliomyelitis vaccine, which can be administered at any time before or after the dengue vaccine.]

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ii) **Receipt of either a blood transfusion or an immune globulin within the recent past:** This is because blood donated by adults in dengue endemic countries is likely to contain dengue antibodies, which could interfere with the replication of the dengue vaccine viruses necessary to induce the required immune responses. The duration that these passively-acquired antibodies persist and hence the period over which they can interfere with the
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vaccine varies\(^6\), but if possible, administration of the live dengue vaccine should be delayed for at least three months.

NB: The above two precautions are not relevant to the inactivated, adjuvanted vaccine.

**False contraindications to dengue vaccination:** The NIC must emphasize that true contraindications to dengue vaccination are rare, and given the potential severity of DHF/DSS in endemic countries, it would be important to use all opportunities to vaccinate. The NIC should also identify the common false contraindications, and emphasize (repeatedly, if necessary) that persons with these conditions could be safely and effectively vaccinated.

**Vaccine administration:** It is assumed that the dengue vaccines should be given by SC injection to children \(\geq 12\) months of age (and to older persons depending upon the funding for catch-up vaccination). However, some vaccine providers might not be familiar with administering SC injections. The NIC would have to make recommendations on the needle size and injection site to be used. (In the United States the upper-outer triceps area is the recommended site for SC vaccination in those aged \(\geq 12\) months\(^6\), whereas in Australia either the deltoid muscle or the anterolateral thigh areas are the recommended sites\(^9\)). Also, in some countries the current NIP does not extend beyond the age when measles-containing vaccine is scheduled (at either nine or 12 months); in these countries, vaccine providers would also have to be instructed about the SC technique in older children. This includes informing vaccine providers on how older children should be held whilst being vaccinated, which may not be as easy as holding an infant still for vaccination.

**Common false contraindications:**

1. Mild intercurrent illnesses, such as diarrhea and mild respiratory tract illness. (Measuring body temperature is not a requirement for assessing well persons for vaccination.)
2. Convalescence from recent febrile illnesses or recent surgery. Indeed, if necessary a policy of vaccination upon discharge from in-patient facilities should be developed and implemented.
3. Current antibiotic (including anti-tubercular) and antimalarial therapy. Antiviral medications used for the treatment or prevention of influenza infections, including both H5N1 and pandemic H1N1, are very unlikely to have any effect on the response to dengue vaccines.
4. A family history of any adverse event following immunization.
5. A past history of dengue, or of DHF/DSS. Also, although dengue vaccination should not be considered as an outbreak response measure (see below), the presence of an outbreak or epidemic of dengue would not contraindicate the use of dengue vaccines.
6. A past history of seizures or any other neurological disorder.
7. Any other chronic medical conditions (except immunosuppressing disease or treatment if a live, attenuated vaccine is used), and
8. A (vaccinee) child is being breastfed or the child’s mother is pregnant.
If the vaccine requires reconstitution, water-for-injection should not be used if (for whatever reason) the vaccine diluent were not available (unless the NIC specifically advises otherwise). The NIC should recommend remedial action if the syringe and needle inadvertently disconnect during vaccination so that less than the standard volume of the vaccine were administered. The usual recommendation in this situation is that the less-than-standard volume not be considered valid, and the person revaccinated with the full standard volume\(^6\). The NIC should also make a recommendation if the vaccine is advertently given by the intramuscular (IM) route; the usual recommendation for live, attenuated vaccines in this situation is that there is no need to revaccinate if a vaccine, meant for the SC route is inadvertently given by IM injection\(^6\) (as it is unlikely that the immune response has been impaired).

There must be safe disposal of all wastes associated with dengue vaccination: needles, syringes, vials, etc. Once administered, the dengue vaccination details - date of vaccination, type of vaccine, batch number, etc. - must be recorded, not only in the personal record book but also in the clinic records.

There should be a mechanism to remind parents or persons to come back to the clinic for subsequent doses of the vaccine. There should also be a mechanism to recall parents or persons to come back to the clinic as soon as is possible for overdue doses of vaccine. How are those children or persons who move from their initial place of residence to another place, even to another endemic country, going to be managed?

The NIC should attempt to integrate dengue vaccination into the NIP as much as possible. For example, if measles-containing vaccine (MCV) is already scheduled in the NIP at 12 months of age, then both the MCV and the first dose of dengue vaccine should be scheduled at 12 months of age, given simultaneously, but in different syringes in different sites. If, for example, MCV and a third dose of Haemophilus influenzae type b (Hib\(^3\)) vaccine are already scheduled in the NIP at 12 months of age, then the MCV, the Hib\(^3\) and the first dose of dengue vaccine should all be scheduled together at 12 months of age. [NB: It must be remembered that MCV and the live, attenuated dengue vaccine should be given either simultaneously (the preferred option) or four weeks apart if possible.]

The NIC should also make recommendations encouraging opportunistic catch-up of other vaccines that are overdue when a child (or older person) presents for dengue vaccination. e.g. if a child who presents at 12 months of age is overdue for a third dose of DTP, a third dose of hepatitis B vaccine and MCV, then these three vaccines should be given simultaneously, in different sites using different syringes, with the first dose of dengue vaccine.
Adverse events following immunization (AEFI)

The NIC should ensure that the AEFI documented in the clinical trials are clearly stated in the national dengue vaccination program resource materials for both vaccine providers and the public. It is likely that local injection-site AEFI, such as swelling, induration and erythema, would be increased following the administration of the adjuvanted vaccine, whereas systemic AEFI, such as fever, myalgia and headache, would be more pronounced after the live vaccine. The parents of young children who are to be vaccinated should be advised on simple measures on how to manage mild to moderate AEFI at home.

The likelihood of increased fevers following the administration of the live vaccine would raise questions about the suitability of using this vaccine in mass campaigns, such as in school-based programs, during the usual dengue-season months. This is because the systemic AEFI could be confused with the symptoms of dengue caused by wild-type viruses, and this in turn, could draw adverse comments and publicity about the vaccine and the programs. However, there might be no other alternative than to go ahead with the campaigns during these months, but the NIC would need to emphasize that although the vaccination may be associated with fevers etc., it has not been shown to ‘cause’ dengue.

As with all vaccines, serious immediate adverse events should be anticipated following administration of dengue vaccines. Fortunately, anaphylaxis following immunization is very rare, and provided that it is managed appropriately, serious sequelae are extremely rare. However, vaccine providers would need to know how to recognize and manage anaphylaxis, they would need to have immediate access to printed management protocols and they would need to have on-hand supplies of adrenaline 1:1000 (containing 1mg adrenaline per mL of...
solution in a 1mL vial) and 1mL syringes with which to administer the adrenaline. They should also have resuscitation skills (and periodically undergo refresher training), and they should know the pathways for the urgent referral of patient with anaphylaxis following the administration of adrenaline and initial resuscitation.

Another immediate AEFI that the NIC would need to highlight is fainting (syncope). This is because it can, albeit infrequently, lead to serious sequelae, notably head injuries\(^\text{11,12}\). Post-vaccination fainting is not uncommon, particularly among adolescents\(^\text{12}\), and hence must be anticipated in any mass dengue vaccination campaigns that target adolescents, especially school-based programs. All vaccine providers delivering dengue vaccines, particularly in school-based programs, would need to be aware of the likelihood of fainting after vaccination, and the appropriate measures that need to be taken. These include:

i) Advising all those about to be vaccinated to remain nearby, under observation, for a minimum of 15 minutes following vaccination

ii) Vaccinating, while in the supine position, those who report either a tendency to faint post-injections or a needle phobia, and

iii) Recognizing a pending faint, and taking immediate steps to get the person into a supine position.

If not already in place, surveillance for AEFI should be considered necessary as part of the NIP, and every effort used in the introduction of the dengue vaccination program to initiate AEFI surveillance. Any serious or unexpected AEFI should be reported to the NIP management or the national body responsible for disease surveillance (see below).
Standard dengue vaccination procedures

The NIC should have previously defined the standard procedures for vaccination, which outline the practical steps to be taken in the vaccination clinic, and which would also apply to dengue vaccination. Effective implementation of these steps is the core of what could be called ‘good vaccination practice’ (GVP).

**These GVP steps are:**

1. **i)** Prior to each vaccination session, checking access to the anaphylaxis management protocols, and that in-date adrenaline 1:1000 and 1mL syringes are readily available. Undertaking the routine (daily) check on the vaccine cold chain temperatures and record them

2. **ii)** Explaining to the parents of children, and to other persons about to be vaccinated, about the risks associated with dengue, the benefits of the vaccine, and the common AEFI

3. **iii)** Performing a routine pre-vaccination assessment to determine if there are any contraindications or precautions to dengue vaccination. If they exist, or there are any uncertainties about whether or not to go ahead with the vaccination, consulting with a local expert in vaccination before proceeding

4. **iv)** Checking if there are any other due or overdue vaccines that should be given opportunistically with the dengue vaccine. If so, ensuring the parent (or person to be vaccinated) is also aware of the risks and benefits associated with the disease(s) and these vaccines

5. **v)** Obtaining consent to vaccinate; provided steps ii), iii) and iv) have been undertaken, verbal consent would be quite acceptable

6. **vi)** Advising parents of children, and other persons about to be vaccinated, on the management of the expected mild to moderate AEFI, and that those about to be vaccinated should remain nearby, under observation, for a minimum of 15 minutes following vaccination

7. **vii)** Checking to ensure that the vaccine (and diluent) about to be given is the correct vaccine (and diluent), that it has not expired and that there is no particulate matter or color change in the vaccine

8. **viii)** Administering the vaccine(s) according to the NIC recommendations

9. **ix)** Disposing of needles, syringes and vials according to current waste disposal protocols

10. **x)** Informing (preferably in writing) parents of children, and other persons about to be vaccinated when the next dose of dengue vaccine would be due

11. **xi)** Documenting the necessary dengue vaccination details according to the requirements set by the NIC, and

12. **xii)** Informing the relevant authority of any significant or serious AE following dengue vaccination.
If not already established, the NIC should task a separate group of experts in immunization practice to function as an advisory service for vaccine providers. This is because in introducing a new vaccine, and not infrequently during the ongoing NIP, vaccine providers experience uncertainties, need second opinions, want reassurance, etc., and in order to cope with these practical complexities there would be a need for this expert advisory service. There might also need to be, particularly in larger populated centres, specialized clinics so that individuals who have experienced a serious AEFI or who have complex medical problems could be referred for assessment for further vaccination, and if so, could be vaccinated under close observation if necessary.13,14

Vaccination strategies

Mention has already been made of the age parameters set by the registration of the dengue vaccine, and of the ages of those eligible for the funded catch-up vaccination program. But how is the vaccine going to be delivered to the different age cohorts of those eligible for vaccination? Again, the NIC would have to consider the capabilities of the current NIP and other issues such as the expected seasonality of dengue, as mentioned above.

The timetable for the roll-out (i.e. introduction) of the dengue vaccination program would have to be carefully designed, as much training and up-skilling of vaccine providers would be required beforehand (see below). The commencement date(s) of the roll-out of the Program would need to be clearly articulated not only to the vaccine providers but also to all other heath care professionals, as well as to the general public. It would have to be decided whether the vaccine will be introduced simultaneously to all parts of the country, or whether regions that are known to be at higher risk for dengue would be given priority initially.

For young children 12-23 months of age dengue vaccination should be ‘added on’ or ‘integrated into’ the existing NIP, and delivered by the same vaccine providers who provide the existing NIP vaccinations. This is because they would presumably be already familiar with the requirements of the NIP, and they would have access to the
consideration should be given to school-based catch-up vaccination programs. Historically, school-based programs were effective in delivering rubella vaccine to adolescent females in many industrialized countries, and more recently this model has been used to deliver hepatitis B and human papillomavirus (to adolescent females) vaccines\textsuperscript{15,16}. Although they may have been in use for some time in developing countries, further innovative evaluations of school-based vaccination programs have recently been reported from southeast Asia\textsuperscript{17,18}.

It would need to be decided, again well in advance, if other (funded) vaccines recommended for school-aged children are to be administered simultaneously with the dengue vaccine at the school-based clinics.

The elements of successful school-based vaccination programs include the following:

1) There needs to be close liaison with the education department and the schools’ authorities. Teachers should be involved as much as is practicable\textsuperscript{15}. The

other NIP vaccines if overdue vaccines are to be given opportunistically with the dengue vaccine. \textbf{For children 24-59 months of age} (i.e. up to the age of entry to primary school) dengue catch-up vaccination could occur through either local (public) clinics or private providers (usually family physicians). The latter providers should have access to the funded vaccine for this purpose, so the families involved would not have to pay for the vaccine. In the local clinics there should ideally be ‘walk-in’ availability of the vaccine with on-the-spot vaccination, but consideration could be given to the desirability and feasibility of campaigns with ‘dengue vaccination days’. \textbf{For school-aged children 5-14 years of age}
dates of the school-based clinics must be agreed upon in advance, and well promoted with the assistance of the schools’ personnel. Parental consent procedures also need to be agreed upon, and teaching staff asked to assist with obtaining consent if necessary.

ii) The program should be implemented by a team of vaccination personnel who are dedicated to the provision of the school-based program. They require back-up support in case of sudden illness in team members, etc. They need to be well aware of vaccination procedures, particularly those that are relevant to school-aged children. They need to know the strategies to prevent fainting, how to manage immediate adverse event, the appropriate documentation and data collection requirements, and the safe disposal of waste. They should have adequate administrative support, they will need transport to and from schools, they need direct communication with the expert advisors (for example, via mobile phones) and they need to be stocked with the necessary consumables and the resources necessary for outreach clinics.

iii) There needs to be a suitable venue for the school-based clinic at each school. This includes space for car parking, with ambulance access (the ambulance services having been informed beforehand about the nature and timetable of the program). There should be adjacent hand washing and bathroom facilities, adequate waiting and recovery room space, adequate space (and desks) for the administrative support personnel, and adequate space for the actual administration of the vaccine.

iv) Arrangements need to be in place for the follow-up of those students who were absent on the vaccination clinic days. It is probably unrealistic to expect the team to return to a school to vaccinate a small number of (previously absent) students; they could instead be referred to a local clinic or private provider to receive the missing dose of vaccine.

v) Feedback should be given to each school’s authorities, detailing any issues of concern that need to be addressed before the visit for the next dose of dengue vaccine, and indicating the performance of the clinic in terms of vaccine coverage.
Training vaccine providers about the dengue vaccination program

All those who are to be involved in dengue vaccination, particularly those involved in the delivery of the (public) funded program, must be up-skilled and trained about the disease, the vaccine and the program. Ideally this training should have been completed prior to the introduction of the vaccination program; it is of the utmost importance if the vaccine is going to be introduced with as few undue concerns, adverse incidents or controversies as possible. The ultimate objective of this training is to ensure that GVP becomes routine practice.

Training resources and programs, that would need to be tailored for the needs of the various vaccine providers (pediatricians, family physicians, community health nurses, health workers) should cover:

i) The disease: a brief description of the virology, immunology and pathogenesis

ii) The vaccine: a description of the nature of the vaccine, its profile, the immunological, safety and efficacy data, the vaccination schedules, the contraindications and precautions to vaccination, vaccine administration (with demonstrations and supervised vaccine administration, if necessary) and possible adverse events following dengue vaccination, and

iii) The vaccine program recommendations: the age parameters set by the registration and the age groups eligible for funded vaccine, a detailed understanding of the dengue vaccine management and cold chain requirements, standard vaccination procedures, strategies for vaccine delivery and the availability of an expert advisory service.

Training would need to continue indefinitely after the program is well established, so as to reinforce GVP, and to ensure that new vaccine providers are well informed and skilled. The experts in the advisory service should keep a log of the concerns about the dengue vaccination program that they had to advise upon. Recurring concerns would need to be addressed in on-going training sessions.
Communications about the dengue vaccination program

A communication strategy to get key messages to all health care providers would need to be developed and implemented. These messages should include the age parameters of the vaccine set by the registration (i.e. that the vaccine is registered for administration for those aged ≥ 12 months of age, with no upper age limit), the ages for the funded primary and catch-up vaccinations, the rollout dates for the commencement of the funded program, whether the funded program would be implemented from the onset either nationally or regionally (and if so, the regions to be vaccinated initially) and the date of cessation of the funded catch-up program.

Another communication strategy would be required for the general public. The public would need to know about the vaccine and that it requires multiple injected doses, the ages of those eligible for funded vaccine and how to access free vaccine if eligible, where to get more information, including approved websites. The public would also need to know when the funded program commences, details of the school-based vaccination programs, dates of any scheduled dengue vaccination days, etc.

There would also need to be a communication strategy to respond to any anti-vaccination claims or media controversies generated about the dengue vaccination program. These claims and controversies should be managed very carefully, as they have the potential to harm the public’s confidence and therefore to cause damage to the program.

Similarly serious AEFI, especially those that either cause death or occur in apparent clusters, should be responded to in an open and confident manner. They should be fully investigated, perhaps utilizing expertise that is independent of the NIC and NIP. It is quite possible that cases of DHF/DSS, triggered by wild-type viruses, could occur in children soon after they have received a first or second dose of a dengue vaccine. Consideration must be given to the responses to these cases, and how the concepts of ‘coincidence’ versus ‘causality’ would be communicated. It would also be important for the NIC to state that it is not appropriate to use the vaccine as a control measure during an outbreak or epidemic of dengue. This is because the vaccination schedule spans six months, and therefore the vaccine could not provide the rapid protection that would be needed to prevent disease in this situation. It would be important that the NIC states this clearly at the outset, so as to be able to manage any public or political pressures to include vaccination as part of the response to the outbreak or epidemic.
Evaluating the dengue vaccination program

Monitoring dengue vaccine coverage:
Consideration should be given on how the uptake of the dengue vaccine would be assessed nationally, regionally and locally.

An indicator that could be used is the percentage (%) of those who have completed the recommended schedule by certain ages:

i) The percentage of children that completed the primary schedule by 2 years of age
ii) The percentage of 2-4 year old children that completed the catch-up schedule by 5 years of age
iii) The percentage of 5-14 year old children that completed the catch-up schedule in their year of the school-based program.

The advantage of this indicator is that it is based on a simple dichotomous outcome: ‘yes’ (fully vaccinated) or ‘no’ (not fully vaccinated); those with missing or inadequate records being defined as not having completed the relevant schedule. The challenge would be to collect this information in a way that is likely to be an accurate reflection of the true uptake, and may require, for example, cross-sectional household surveys.

As well as coverage, it would be useful to assess apparent wastage of the funded vaccine, by comparing vaccine distribution data with discard data (e.g. expired vaccines, and vaccines that have been exposed to significant cold chain aberrations) and coverage data. This information might give some indication of the degree of leakage of funded vaccine from the funded public program to those ineligible for the free vaccine via the private sector.
Surveillance of dengue: Decisions would have to be made about surveillance for dengue; indeed these decisions should have been made well before the introduction of the dengue vaccination program. Is the surveillance to be national, regional or only in selected sentinel sites? What are the case definitions used for surveillance, and is there adequate laboratory capacity for the surveillance? Is there surveillance for not only the clinical syndromes, but also the infecting serotypes as well?

Several other issues deserve consideration. Once the vaccine is being administered in the funded program, would there be the capacity for enhanced surveillance of those cases in the age groups eligible for free vaccine? What is the vaccination status of the cases of dengue, and of DHF/DSS? What are the infecting serotypes? Are vaccine failures occurring? If so, is there any evidence of serotype-specific failures? Could observational studies be used to measure the vaccine’s effectiveness in the country’s program? What changes occur in the epidemiology of dengue and DHF/DSS in the country following the introduction of dengue vaccination?

Surveillance of adverse events following dengue vaccination: Surveillance for serious and unexpected AEFI should be considered as inherent to the NIP. The relevant authority should collate this data, and prepare periodic reports for the NIC.

Severe adverse events immediately following immunization, in particular anaphylaxis and injury resulting from a faint (syncope) should be further investigated. Similarly other serious or unexpected AEFI that could plausibly be causally-related to immunization should be further investigated. DHF/DSS and other severe syndromes or complications of dengue occurring in vaccinated persons should be considered as AEFI.


References (cont.)


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