Urging for Immediate Action in Dengue Vaccine Approval

Historically, Malaysia was foremost to document Dengue Fever (DF) in 1902 and Dengue Haemorrhagic Fever (DHF) in1962. It would have been another feather in our national cap if the dengue vaccine had been licensed for use, but instead as reported, the minister and the regulatory authorities have dragged their feet on the approval of the dengue vaccine. 11 countries including our ASEAN neigbours Singapore, Indonesia, Thailand and Philippines have since licensed the vaccine.

Every Malaysian can identify with a family member, friend or someone who has had dengue, was hospitalised for it, suffered from complications of the disease or succumbed to the disease syndrome. It cuts across the economic divide and social strata. In more tangible terms, as of 1 October 2016, 83,224 cases were notified with 186 deaths. This is a welcome reduction from the preceding period in 2015, but nonetheless most disconcerting.

Translated into monetary terms, Malaysia spent an estimated RM735 million on dengue management and vector control. Two think tanks have estimated that Malaysia can reduce the economic burden of dengue by 50% if it approved the dengue vaccine.

The long awaited dengue vaccine is therefore a most welcome breakthrough. Though the overall efficacy (60.8%) is not as high as the efficacy of most paediatric vaccines we are familiar with, the dengue vaccine nonetheless demonstrates a profile of clinical efficacy, which makes it worth considering for licensure.

The two large multi-center studies in Asia (including Malaysia) and Latin America showed that the administration of the novel quadrivalent dengue vaccine in healthy children reduced the rate of dengue related hospitalisations by 67% and 80.3% respectively, which would definitely reduce the demand on our hospitals beds.

The dengue vaccine also reduced the severity of the disease by 88.5% and 95.5% in the two landmark trials. Both the reduction in hospital admissions and severity of the disease would further ease the economic burden of dengue and more Malaysians would be spared the morbidity (illness) and mortality (deaths) from the disease.

Another aspect of the vaccine, which is equally important, is that no serious adverse events were reported in either of the trials.

Virtually, all of the vaccine programs in Malaysia were initially driven by doctors in the private setting prior to its inclusion into the National Immunisation Program (NIP). Hepatitis B, MMR, Haemophilus influenza B, Human Papilloma Virus (HPV) and other vaccines were prescribed by private practitioners prior to their inclusion into the NIP in 1989, 2002, 2002, 2010, respectively. Others yet to be incorporated into the NIP like the Pneumococcal Conjugate Vaccine (PCV), Rotavirus (RV), Varicella, Influenza vaccines, etc, are presently widely used by private practitioners, whilst the Ministry of Health (MOH) consider the cost implications. And I suspect it would be no different with the dengue vaccine. But why the hesitancy by the regulatory authorities to license its initial use by the private practitioners in Malaysia?

Immunogenicity data from phase II studies (CYD22 in Vietnam and CYD 47 in India) suggest that the population 18 years of age and above in endemic areas responded

well to the dengue vaccine. The antibody responses (GMTs) after the third injections were generally higher than those seen in the CYD14 and CYD15 study population (2-16 year old) in which efficacy was demonstrated. Since the GMTs were non-inferior compared to those in the efficacy trials, it is anticipated that adults up to the age of 45 years old living in endemic areas will have similar levels of protection, if not better, when compared with the 9-16 year old population.

Dengue sero-positivity has been shown to increase with age in Malaysia, approximating 90% at 60 years old. These "older" cohorts, previously infected with dengue, produced higher sero-conversion rates and broad neutralising antibodies with the dengue vaccine, which would therefore confer better protection from the disease. The minister's concern is therefore not based on sound immunological science.

I suspect one of the reasons lies with the fact that this is the first time usage of a vaccine prior to its licensing by well established regulatory authorities eg FDA in the USA and the EMEA in Europe. But why should we be beholden to other regulatory authorities and not be the pathfinders in a disease epidemiology unique to our geography?

The other reason I think is the concern for the lack of Post Marketing Surveillance (PMS) and pharmacovigilance infrastructure and processes in the country. It must be emphasised that long term effectiveness and rare adverse effects can only be captured within the context of "real world usage" and not within the confines of further clinical trial numbers. Let us therefore contribute to the "dengue real world experience" instead of just "being spectators" & "playing safe".

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For further reading:
http://www.thesundaily.my/node/405930
http://www.themalaymailonline.com/malaysia/article/think-tanks-vaccine-can-save-half-of-malaysias-rm735m-dengue-cost