LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

PUBLIC HEALTH CRITERIA FOR DENGUE VACCINE RISK/BENEFIT ASSESSMENT AND RISK MANAGEMENT

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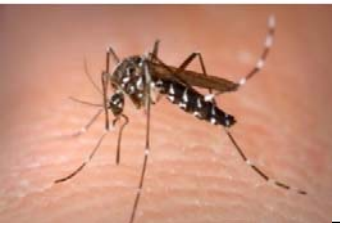

PUBLIC HEALTH CRITERIA FOR DENGUE VACCINE RISK/BENEFIT ASSESSMENT AND RISK MANAGEMENT

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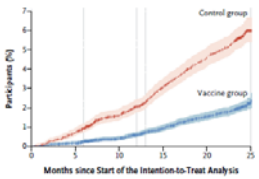
- ***Public health considerations on vaccine deployment, with special reference to Dengvaxia®***
- ***Challenges for evaluating dengue vaccines in the pipeline***

Public health decisions on the use of Dengvaxia® are complicated by several characteristics of the vaccine that became apparent in the Phase 3 trials.

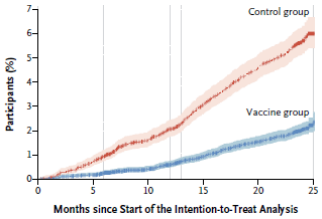
- **Vaccine is only partially efficacious and has lower efficacy than many other vaccines that are in use against other diseases.**
  - But, other vaccines have partial efficacy against target diseases (rotavirus, RTSS/AS01) but have substantial public health benefit.
  - There is population acceptance of partial efficacy vaccines (rotavirus against severe diarrhoea, pneumococcal vaccine against pneumonia).
  - **The primary endpoint (virologically-proven dengue disease) was only measured for 2 years from dose 1, and there is uncertainty as to the duration of protection from the primary course and whether booster doses will be required.**
  - Not uncommon for decision on use of a vaccine to be taken when only limited information on duration of efficacy and in absence of information on need for booster doses.



Some vaccines have an age window for severe disease through which protection is primarily required (rotavirus, pneumococcal) but this is less the case for dengue for which individuals may be at risk for long periods.

Public health decisions on the use of Dengvaxia®

- **Decisions on the cost-effectiveness of vaccine introduction are likely to be based on the predicted long term impact of the vaccine, which can currently be assessed by mathematical modelling studies, but based on assumptions of uncertain validity, including about duration of protection.**
  - But this is true for most newly introduced vaccines!
  - Important to monitor long-term performance of vaccine in routine use (easier stated than done in absence of serological correlate of protection!).



Public health decisions on the use of Dengvaxia®

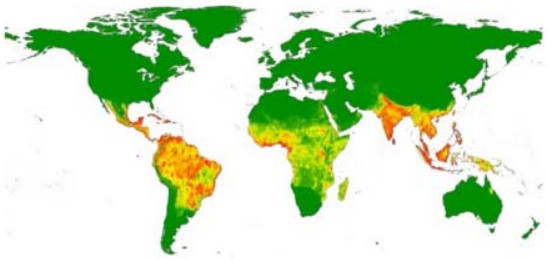
- **The 3-dose schedule, with doses separated by 6 months, will be challenging to administer to ensure that all receive the full course.**
  - The safety consequences of not receiving the 2nd and 3rd doses are unknown.
  - There is uncertainty about the contribution of the 2nd and 3rd doses towards efficacy, which has cost implications.
- **There were safety signals in the Asian Phase 3 trial that included children under the age of 9 years, especially under the age of 5 years, in terms of an increased risk of hospitalised and severe dengue in the 3rd year after the start of vaccination. Thus licensing has been confined to 9 years and above, where no safety signals were seen in either the Asian or Latin American Phase 3 trials.**
- **There is evidence that efficacy may be absent, or lower, in children who had not been infected with dengue prior to vaccination, and the apparent safety signal in those under the age of 9 years may be related to the fact that a higher proportion of these children had not been exposed to dengue prior to vaccination, compared to children in older age groups.**

Public health decisions on the use of Dengvaxia®

- **Major beneficial effect of the vaccine likely to be in those previously infected with dengue, but currently there is no simple point of care test to identify such persons.**
- **Vaccination strategies are likely to include both seropositive and seronegative persons. The latter group may derive little benefit from vaccination and might in the longer term suffer an increased risk of dengue as a consequence of vaccination.**
  - Some parallels with mass BCG vaccination campaigns in the 1970s.
- **Because the vaccine is likely to be most beneficial in population in which a substantial proportion or persons has been previously infected with dengue, sub-national implementation is likely to be the best utilisation strategy in most countries. However, defining the target populations will present significant challenges.**
  - Ideally need local knowledge on age specific dengue seroprevalence – but not available in many places, so surrogate measures will need to be derived.

Public health decisions on the use of Dengvaxia®

- **The vaccine has been developed for use in low and middle income countries, and there is therefore no safety database from routine use of the vaccine in high income countries with more developed pharmacovigilance systems to detect adverse effects.**
  - This is unlike the situation for other recently introduced vaccines (rotavirus, pneumococcus, HPV), but similar to the situation to RTSS/AS01 and the Meningitis A vaccine.
  - Increased importance of
    - good pharmacovigilance systems in at least some of the countries where vaccine introduced early
    - well designed and executed post-licensure studies



Lessons and challenges for evaluating dengue vaccines in the pipeline

- **Need to collect and store serum samples in order to be able to measure prior dengue status on all trial participants prior to vaccination.**
- **Need to plan active follow-up to detect dengue cases for more than 2 years after vaccination.**
- **Need to address the ethical challenge of conducting placebo-controlled trials, particularly in the situation where an existing vaccine is already licensed in the country where trial is taking place**. *(see Rid A, Saxena A, Baqui AH, et al. Placebo use in vaccine trials: Recommendations of a WHO expert panel. Vaccine 2014)*
- **Or, deal with the complexity of trials involving head-to head comparisons.**