GVIRF 2016: Comprehensive assessment of risks and benefits of vaccines: the example of dengue (Workshop 2)	
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Session Outline	**Chairs:** Lucky Slamet and Stephen Thomas **Opening remarks:** Lucky Slamet **Presentations:** Stephen Thomas (WRAIR): Dengue vaccines: status update Peter Smith (LSHTM): Public health criteria for dengue vaccine risk/benefit assessment and risk management. **Discussants:** Gandi Rayón Ramírez (COFEPRIS) Chris Nelson (Sanofi Pasteur) Kwasi Amfo (Takeda) Alex Precioso (Butantan) Hasitha Tissera (Sri Lanka MOH) **Closing Remarks**: Stephen Thomas
Objectives of the session	*To discuss:* • Provide a status update on the dengue vaccine pipeline; • With specific reference to dengue vaccines, discuss regulatory vs. public heath criteria in relation to risk benefit assessment; • Discuss risk management and post-licensure studies as tools to further monitor new vaccines and answer scientific questions remaining at the time of registration.
Main outcome	• Participants updated on the dengue vaccine pipeline and benefit/risk considerations
Summary (400-500 words)	Dengue vaccine development has been hampered by a number of challenges, including four distinct serotypes with potential to immunologically enhance, no known correlate of protection, no validated animal model of disease, and challenges in measuring neutralizing antibody with available immunoassays. There are several candidates in clinical development, including one vaccine that has been licensed in a number of endemic countries, CYD-TDV (Dengvaxia®) by Sanofi Pasteur. Two other vaccine candidates have recently begun or are expected to soon begin Phase 3 trials, and three others are in Phase 1 trials. The licensed vaccine as well as the two other most advanced candidates are all live attenuated (live recombinant) vaccines. Common to all candidates is a higher immune response in trial participants who have already been exposed to dengue prior to vaccination (seropositives) compared to those subjects who are unexposed at baseline (seronegatives). In the Phase 3 efficacy trial of CYD-TDV the immune response was paralleled by higher efficacy in seropositives compared to seronegatives and higher efficacy against hospitalized and severe dengue during the first two years of the study. This as well as other attributes of dengue vaccines will be important for

	countries making decisions about vaccine introduction, many of which are lower-middle income countries. Many vaccines, including those for dengue, malaria, and rotavirus are partially efficacious vaccines, yet still may have substantial public health benefit. As with all new vaccines, there are a number of remaining questions at the time of licensure. While the benefit/risk may be evaluated by regulatory authorities from clinical trials data, continued investigations are needed post-licensure to ensure highest benefit in endemic countries is achieved with available tools and resources. This is particularly relevant to vaccines showing variable performance characteristics in different population groups, as the case for dengue vaccines. One hypothetical concern for dengue vaccine development for all candidates in the pipeline has been a risk of vaccine-associated dengue due to partial or waning immunity that could mimic that seen with secondary natural infections. In the first Phase 3 trial of a dengue vaccine, an elevated risk of hospitalized and severe dengue was seen in the youngest age group, and this age group was thus not included in the indicated age range. While no safety signals were identified in other age groups in the trials, post-licensure studies are important tools to confirm the benefit/risk seen in the trials for any vaccine candidate that becomes commercialized. Longer-term surveillance for dengue must be linked to good vaccination records. In this way, vaccine effectiveness and safety are closely linked. Post-licensure studies that further elucidate questions around duration of protection, longer-term safety and effectiveness (including with fewer than the recommended doses), and routine pharmacovigilance are important for the continual benefit/risk assessment that occurs throughout a product lifecycle and informs policy to maximize the benefit to public health.
Key references or quotes (up to 5)	Vannice KS, Durbin A, Hombach J. Status of vaccine research and development of vaccines for dengue. Vaccine. 2016 Mar 10. pii: S0264-410X(16)00293-0. doi: 10.1016/j.vaccine.2015.12.073. [Epub ahead of print]