

Long-term safety assessment of live attenuated tetravalent dengue vaccines

Introduction

WHO estimates that approximately 2.5 billion people are at risk from dengue, and 50 to 100 million dengue infections occur annually. 500,000 of those are severe dengue cases who require hospitalization.

There is no licensed dengue vaccine and prevention is exclusively through vector control. However, several vaccine candidates with a variety of vaccine constructs are in the pipeline with the most advanced being a live attenuated chimeric vaccine (developed by sanofi pasteur) that employs the yellow fever 17D-backbone which is currently in Phase III trials in Asia and the American region.

WHO held an expert consultation in October 2011 to review long-term safety considerations of dengue vaccines, and in particular the current scientific evidence regarding a hypothetical concern (based on the natural history of dengue) of an increased risk of severe dengue resulting from vaccination with the live attenuated vaccine. The experts convened also considered broadly various methodological approaches that could potentially be used for the long-term assessment of vaccine safety.

Safety issues

It has long been recognized that infection with a specific DENV serotype (of the 4 distinct serotypes) produces life-long serotype-specific immunity whereas immunity against the other serotypes is short-lived for about 3 to 6 months. Severe disease occurs most commonly after secondary infections and the most important risk factor is infection with a different serotype than the previous infection(s). There is additional evidence of an increased risk of severe disease in dengue-infected infants born to dengue-immune mothers associated with decline in maternally-derived neutralizing antibodies. While mechanisms for this increased immunopathology are not well understood, non-neutralizing antibodies or sub-neutralizing antibody titres are believed to constitute a critical element. To date, clinical trials have not observed an increased risk of severe dengue following vaccination. In addition, trials to date have shown the live dengue vaccine candidates to be well-tolerated (some studies showed more local and systemic reactions after the first dose than subsequent doses and more frequent fever than in adults) and have not reported dengue-like illness caused by the vaccine.

Current WHO guidelines and considerations for future assessments

Previous WHO guidelines for the clinical evaluation of dengue vaccines in endemic areas (2008), and guidelines on the quality, safety and efficacy of live attenuated tetravalent dengue vaccines (2012) have recommended follow-up of dengue-vaccinated and control subjects for at least 3 to 5 years after completion of primary vaccination in Phase II and Phase III trials. Ongoing clinical trials for candidate vaccines take into account this WHO guidance, however, post-licensure vaccine introduction strategies may need to include longer-term assessments in order to extend and provide more robust safety (and effectiveness) data.

The WHO consultation discussed a number of methodological considerations, including factors for or against the potential use of case-control, cohort, randomised control or stepped wedge study designs. Key issues to be considered in selecting an appropriate study design and planning long-term studies will include the feasibility of accurate ascertainment of vaccination status and infection exposure, the ascertainment of severe dengue and diagnostic challenges, a need to conduct studies in a variety of settings with different dengue transmission intensities, and ethical challenges for including unvaccinated comparison groups in long-term studies after an effective vaccine is licensed.

Key conclusions of the expert consultation included that (a) reliable data on the long-term safety of dengue vaccines will be critical to identify and manage unsubstantiated safety concerns that could emerge after vaccine introduction; (b) a coordinated approach should be established to ensure such safety assessment (most likely in sentinel sites); (c) efforts should be made to enhance dengue surveillance in countries where the vaccine is introduced given that cases of severe dengue are less likely to be captured by the current adverse event surveillance systems in many endemic countries; (d) dengue vaccine introduction provides an opportunity to further strengthen routine post-marketing surveillance of AEFI (e.g., through the Global Vaccine Safety Initiative); and (e) the collection and long-term storage of serum or other samples from vaccinees should be encouraged to facilitate further studies (e.g. for correlates of protection and possible booster needs). It was also noted that close collaboration will be needed between licensing national regulatory authorities and with respective vaccine sponsors.

A more detailed report of the consultation has been accepted for publication.