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World's most advanced dengue vaccine candidate shows promise in phase 3 trial

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The first dengue vaccine candidate (CYD-TDV) to reach phase 3 clinical testing has shown moderate protection (56%) against the disease in Asian children, according to new research published in *The Lancet*.

Dengue is a mosquito-borne disease that infects around 390 million people each year, of whom about 96 million suffer from symptomatic infection. WHO estimates that the global burden of dengue has risen 30-fold over the past 50 years, with over half of the world's population at risk of the disease.

There is no licensed vaccine available to treat or prevent dengue fever, and efforts to develop one have been complicated by the fact that dengue is caused by four distinct dengue viruses, and a vaccine must target all four serotypes (DENV 1–4).

This phase 3 trial took place in dengue-endemic areas across five countries in Asia, a region that accounts for over 70% of the global dengue burden. The study involved 10 275 healthy children aged 2 to 14 years who were randomly assigned to receive three injections of the CYD-TDV vaccine (6851) or a placebo (3424) at 0, 6, and 12 months, and followed for up to 2 years.

The researchers recorded 250 dengue cases more than 28 days after the third injection—117 in the vaccine group and 133 in the placebo group, demonstrating an overall protective efficacy of 56.5%.

The vaccine also showed 88.5% efficacy after 3 doses against severe disease (dengue haemorrhagic fever) which leads to hospitalisation for over half a million people (mostly children) every year, and 67% against dengue-associated hospitalisation.

The researchers found that the vaccine gave low protection (35%) against DENV 2, but more than 75% protection against DENV 3 and 4, and 50% against DENV 1.

The vaccine was generally well tolerated. A total of 647 serious adverse events were reported, 402 (62%) in the vaccine group and 245 (38%) in the placebo group.

According to lead author Dr Maria Rosario Capeding from the Research Institute for Tropical Medicine in the Philippines, "Our results suggest that vaccination with CYD-TDV can reduce the incidence of symptomatic dengue infection by more than half and importantly reduced severe disease and hospitalisations. This candidate vaccine has the potential to have a significant impact on public health in view of the high disease burden in endemic countries."

Writing in a linked Comment, Professor Annelies Wilder-Smith from Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore says, "Perhaps the most interesting finding of this trial was that efficacy after at least one dose was almost as high as that after three doses…Because three doses 6 months apart is an inconvenient and costly immunisation schedule for scale up in national programmes, the question of whether sufficient efficacy can be achieved with a lower number of doses deserves further assessment."

She adds, "With an estimated 96 million clinically apparent dengue infections annually, a reduction by half would present a significant public health benefit that would support dengue vaccine

introduction….Whether the armamentarium of alternative vaccine candidates presently in the pipeline (including inactivated, live attenuated, chimeric, recombinant, subunit and DNA vaccines) will improve efficacy beyond 56% remains to be established. For the moment, the CYD-TDV vaccine is the best we have; however, with 56% efficacy it will never be a single solution. Continued support for the development of other novel strategies including drugs, improved case management, insecticides, and new approaches to vector control, is needed before effective dengue control becomes a credible prospect."

Provided by Lancet