Single-dose dengue vaccine protects 79.6% of those vaccinated, study shows

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Batch used to validate the vaccine's production process at the Butantan Institute. Credit: André Ricoy/Comunicação Butantan

A single-dose dengue vaccine produced by Butantan Institute in São Paulo state (Brazil) prevents development of the disease in 79.6% of

those vaccinated, according to an article published in *The New England Journal of Medicine*.

Called Butantan-DV, the vaccine contains attenuated versions of all four dengue virus serotypes. The results of the ongoing Phase 3 trial show that it is safe and effective for all age groups between 2 and 59, and for people with or without a prior history of infection by dengue virus.

"Publication of the article in the world's leading medical journal attests to the rigor and quality of the work done by researchers at 16 Brazilian centers located in all five regions of the country, and coordinated by Butantan Institute," infectious disease specialist Esper Kallás, first author of the article, told Agência FAPESP. "In June, we'll complete the five-year follow-up period. Once the data has been consolidated, we'll know how long the protection induced by the vaccine will last."

Also according to Kallás, who heads Butantan Institute, the researchers plan to submit a report to ANVISA, Brazil's health surveillance agency, in the second half of this year in order to apply for registration of the vaccine.

"If all goes well, we'll win definitive approval for the vaccine in 2025. We already have the infrastructure to produce it at Butantan Institute, although it can still be perfected. After all, it's tetravalent, corresponding to four vaccines in one," he said.

The article published today describes the results of the first two years of the Phase 3 clinical trial, which began in February 2016 and involves 16,235 participants in 13 states. Preliminary data disclosed by Butantan Institute in December 2022 pointed to overall efficacy of 79.6%. The results for each subgroup evaluated have now been detailed.

Vaccine efficacy was 80.1% for participants aged 2-6, 77.8% for those

aged 7-17, and 90.0% for 18-59 age group. Stratification by serological status showed protection for 73.6% of participants with no evidence of prior infection by dengue virus and 89.2% of those previously exposed to the virus. Efficacy was 89.5% against dengue serotype 1 (DENV-1) and 69.6% against serotype 2 (DENV-2).

It was not possible to assess the vaccine's efficacy against serotypes 3 and 4 because they were not circulating during the follow-up period. Most adverse side effects were classified as mild or moderate. The main reactions were pain and redness at the injection site, headache, and fatigue. Severe adverse events relating to the vaccine were recorded for under 0.1% of all those vaccinated, and all of them recovered.

"Findings from Phase 2 [the previous clinical trial] showed that the four attenuated viral serotypes in Butantan-DV multiply in the human organism and induce a balanced response in terms of antibody production. This leads us to conclude that its efficacy against DENV-3 and DENV-4 will also be good," said virologist Maurício Lacerda Nogueira, one of the coordinators of the trials.

"It should be stressed that Butantan Institute's vaccine has also proved extremely safe for people who have never had dengue, which is an advantage over the vaccines now available on the market. Furthermore, it can be administered to a broader age group and a single dose is sufficient." Nogueira is a professor at the São José do Rio Preto Medical School (FAMERP), one of the centers that are running the trials.

Two dengue vaccines have been approved in Brazil to date. One is Dengvaxia, produced by Sanofi Pasteur. This vaccine requires three applications and is indicated for people aged 9–45 who have had dengue. The other is Qdenga, produced by Takeda. Application in Brazil will begin this month, for people aged 4–60, regardless of serological status. Two doses will be needed for full immunization in this case.

Butantan-DV's single-dose scheme has several advantages, the authors write in the article. In addition to the logistical and economic benefits, rapid protection may be important in the event of an outbreak and for travelers without immunity to places where the disease is endemic.

In Brazil, dengue is considered hyperendemic, meaning its high prevalence remains constant from one year to the next. According to the Health Ministry, 1.6 million probable cases were notified in the first 11 months of 2023. So far this year, the number of probable cases has reached 217,841, according to data disclosed on Tuesday, January 30. Fifteen deaths have been confirmed, and 149 are under investigation. Based on these numbers, the current incidence rate in Brazil is calculated as 107.1 cases per 100,000 inhabitants, and the fatality rate is 0.9%.

Secondary benefits

Development of the tetravalent dengue vaccine began at Butantan Institute in 2010, using a formulation created by researchers affiliated with the US National Institutes of Health (NIH). Clinical trials in Brazil began in 2013, under the aegis of the project "Development of a tetravalent dengue vaccine," led by Neuza Frazatti Gallina, winner of the 2023 Péter Murányi Prize. The Phase 3 trial, which is set to end in June, may be the largest clinical trial of a vaccine ever conducted solely in Brazil.

"The cost of dengue in Brazil is absurd," Nogueira said. "The vaccine is expected to reduce mortality and hospitalizations due to the disease, so investment of several hundred million reais by the Brazilian government in the development of an indigenous vaccine will have a huge impact on public health.

"Secondary benefits can already be observed. The scientists in charge of the trial reported in the article conducted clinical trials of CoronaVac

during the COVID-19 pandemic. So we were prepared. Formation of this vaccine research network is a valuable achievement that the Brazilian government must preserve. It will enable us to respond rapidly to future challenges of a similar kind."

More information: Esper G. Kallás et al, Live, Attenuated, Tetravalent Butantan–Dengue Vaccine in Children and Adults, *New England Journal of Medicine* (2024). DOI: 10.1056/NEJMoa2301790

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