QUICK EVIDENCE SYNOPSIS

Title: Efficacy and Safety of Vaccines for Dengue

Date completed: April 22, 2015

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Clinical question: What are the efficacy and safety of dengue vaccine in children and adults?

What does the evidence conclude?

Intervention	Quality of Evidence[a]	Balance between Benefits and Harms[b]
Three injections of recombinant live attenuated tetravalent dengue vaccine (CYD-TDV)	Moderate	Likely to be beneficial for children Unknown effectiveness for adults

[a]Quality of evidence scale (GRADE): high, moderate, low, and very low. For more information on the GRADE rating system, see http://www.gradeworkinggroup.org/index.htm.
[b]The Guideline Elements Model, http://gem.med.yale.edu/default.htm.

What are the parameters of our evidence search?

PICO:

Population	Healthy children and adults
	Patient demographics, country of residence, socioeconomic status; nutrition status, morbidity, dengue serostatus at baseline
Intervention	Live attenuated virus, including monovalent DENV1-4, bivalent (DENV1 and 3 or DENV2 and 4), or recombinant, live, attenuated, tetravalent dengue vaccine (CYD-TDV)
	DNA, including D1ME or TVDV
	Purified, inactivated virus, including DENV-1 PIV or TDENV-PIV
	Subunit, including DEN1-80E or V180
	Vaccine dose, frequency, duration (protocol), combinations
Comparator	Placebo, no vaccination
Primary outcome(s)	Incidence of dengue disease (virologically confirmed according to the CDC case definition), severity of illness, infecting serotype, dengue serostatus
	Mortality
	All harms

What is the basis for the conclusion(s)?

Population: Healthy children aged 2-14 years
Setting: Outpatient
Intervention: Three injections of recombinant live attenuated tetravalent dengue vaccine (CYD-TDV)
Comparator: Placebo

What do clinical guidelines say?

We found no relevant guidelines.

Author commentary: The clinical question about the efficacy and safety of dengue vaccine in children was explored in four double-blind, industry-sponsored RCTs.[1–4]

No studies examined dengue vaccine in adults. Moderate-quality evidence from our meta-analyses suggests that three injections of recombinant live attenuated tetravalent dengue vaccine (CYD-TDV) prevent 25 cases of virologically confirmed dengue per 1000 patients treated (**Table 1**). The vaccine was no better than placebo in improving survival; however, trials did not have a statistical power to detect differences in mortality. Higher efficacy was observed in children who were seropositive at baseline (data not shown).[1]

Low-quality evidence indicates that the vaccine results in a statistically significant reduced relative risk of severe hemorrhagic fever (vaccine efficacy 76% for severe dengue and 65% for hemorrhagic dengue) but no statistically significant reduction in absolute risk difference (data not shown). High-quality evidence suggests that vaccine does not cause serious adverse effects, and published RCTs suggest that it does not carry an increased risk of allergic reactions. In fact, the risk of other acute viral and bacterial infections is lower in vaccinated children (relative risk 0.8, 95% CI 0.6; 0.9).[1] However, long-term safety of the vaccine has not yet been established in the literature after 25 months of follow-up in the studies.

The quality of evidence from double-blind RCTs was considered lower due to statistical heterogeneity in the results. Because the number of RCTs was small, we could not explore heterogeneity and attribute it to known study or patient characteristics.

These results are applicable to children in Latin America and the Asia-Pacific region where the trials were conducted. The effectiveness of dengue vaccine in adults and in people who travel to endemic areas from elsewhere is unknown. The Food and Drug Administration (FDA) has not yet approved dengue vaccine in the United States. We found no guidelines regarding vaccine for dengue.

FDA Black Box warning

FDA precautions and warnings: [Add if applicable and link to Gold Standard?]

Glossary: AGREE II, Appraisal of Guidelines for Research and Evaluation; CDC, Centers for Disease Control and Prevention; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NNT, number needed to treat; NNTp, number needed to treat to prevent one event; NS, not statistically significant (null hypothesis of no difference between intervention and comparator cannot be rejected; therefore, vaccine effects do not differ from placebo effects); RCT, randomized controlled trial; RR, relative risk.

Next scheduled update: Literature monitoring will provide additional insight to update scheduling. Since updates are conducted at a minimum of every 2 years, this evidence review should be updated no later than April 2017.

TABLE 1 Efficacy and Safety of Vaccines for Dengue

Outcome	Risk with Intervention per 1000	Risk with Comparator per 1000 Attributable Events per 1000 Treated (95% CI)	Relative Risk (95% CI) NNT (95% CI)	Number of Participants (RCTs)	Quality of Evidence (GRADE)	Comment
Mortality	0.4	0.9	RR 0.5 (0.1; 3.4)	35,396 (four RCTs)[1–4]	Low	No difference
Virologically confirmed dengue (VCD) (any severity)	**26 Vaccine efficacy[a] 58%**	**62 Attributable avoided events per 1000 treated 25 (5; 44)**	**RR 0.5 (0.3;0.6) NNTp 40 (23;200)**	**35,396 (four RCTs)[1–4]**	**Moderate**	**Favors vaccine**
Serious adverse events due to vaccine	55	63 attributable avoided events per 1000 treated 8 (1; 16)	RR 0.9 (0.8; 1.0)	35,396 (four RCTs)[1–4]	High	No difference

[a]We calculated vaccine efficacy defined as the reduction in the incidence of a disease among people who have received a vaccine compared with the incidence in unvaccinated people.
CI, confidence interval; *NNT*, number needed to treat to achieve one event; *NNTp*, number needed to treat to prevent one event; *NS*, not statistically significant (null hypothesis of no difference between intervention and comparator cannot be rejected; therefore, vaccine effects do not differ from placebo effects); *RCT*, randomized controlled trial; *RR*, relative risk.

REFERENCES

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Recommended citation: Shamliyan TA, Goldmann DR; Elsevier Evidence-Based Medicine Center: Evidence Review: Efficacy and Safety of Vaccines for Dengue. Publication date: April 22, 2015. Access date: April 28, 2015.