Public Health Impact and Cost-Effectiveness of a New Dengue Vaccine (TAK-003) With a Large Catch-Up Cohort in Puerto Rico

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INTRODUCTION

- Dengue is a vector-borne viral infection primarily transmitted between humans through the mosquitos of the species *Aedes aegypti* and *Aedes albopictus*
- Symptoms range from a mild flu-like illness to severe debilitating disease that can last for several weeks; although uncommon, the most severe cases can result in hospitalization and death regardless of serostatus
- There is no proven effective treatment for dengue and clinical care is supportive. Prevention of dengue by vaccination is key to reduce dengue burden
- Although dengue is rare in the contiguous United States, it is endemic in some US territories, with more than 95% of dengue cases reported between 2010 and 2020 being identified in Puerto Rico (n=29,862)
- In the pivotal phase 3 study (DEN-301), the tetravalent vaccine TAK-003 was shown to be generally well tolerated and highly efficacious at preventing dengue and associated hospitalizations
- The only licensed vaccine for dengue in Puerto Rico is CYD-TDV, but given its requirement for serological prescreening (cannot be used in seronegative individuals), the pilot program of CYD-TDV in Puerto Rico is expected to have limited impact on dengue prevention due to limited uptake

OBJECTIVE

- The aim of this study was to investigate the public health impact and cost-effectiveness of vaccination with TAK-003 with large catch-up cohorts in Puerto Rico compared with no vaccination

METHODS

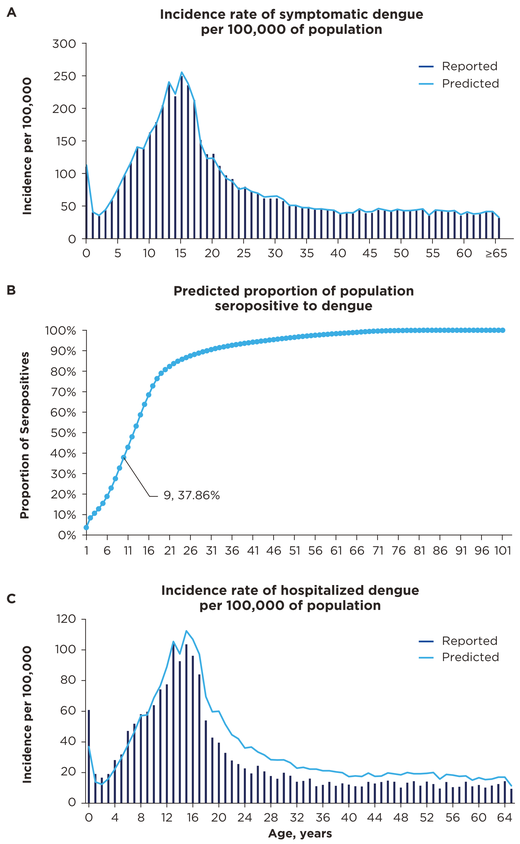
- A dynamic transmission model was developed with age-structured host population, explicitly modeled vector population, age-specific force of infection, up to 4 serotype-specific dengue infections, and key elements of the dengue natural history (cross-protection, increased risk of clinical and hospitalized disease with second infections)
- Vaccine efficacy was derived from the phase 3 DEN-301 trial and extrapolated over the study time horizon
- The model was fitted to the average annual incidence of symptomatic dengue in Puerto Rico, estimated based on the number of confirmed and probable dengue cases reported between 2010 and 2020 (underreporting was applied)
- Epidemiological, cost, and quality of life inputs were derived from data specific to Puerto Rico where possible
- Cost-effectiveness analyses were conducted using a societal perspective, whereas costs were calculated and adjusted to 2022 US dollars and included all direct and indirect costs differentiated by age at disease onset
- The cost of TAK-003 was set to an illustrative price of $154 per dose, with the vaccine administration cost set to $17.04 per procedure
- The vaccination strategy explored was routine at age 4 with catch up from age 5 to 18 administered in a 2-dose series, with an 80% coverage of all eligible children

RESULTS

MODEL FITTING TO THE EPIDEMIOLOGY OF DENGUE IN PUERTO RICO

- The reported age-specific incidence rate of symptomatic dengue in Puerto Rico was well replicated by the model in the absence of vaccination (**Figure 1A**)
- The model predicted seroprevalence at age 9 of 37.9%, which is in line with reported seroprevalence for Puerto Rico in the literature (**Figure 1B**)
- Although the model overestimated the incidence of hospitalizations in individuals aged 15 years and older, and underestimated this rate in newborns, the shape of the age-specific incidence curve was similar to reported data (**Figure 1C**)

FIGURE 1: RESULTS OF SIMULATION WITHOUT VACCINATION: (A) INCIDENCE RATE OF SYMPTOMATIC DENGUE BY AGE (REPORTED VS PREDICTED), (B) PREDICTED SEROPREVALENCE BY AGE, AND (C) INCIDENCE RATE OF HOSPITALIZED DENGUE BY AGE (REPORTED VS PREDICTED)



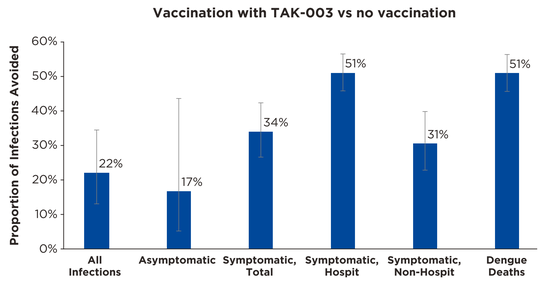
PUBLIC HEALTH IMPACT OF VACCINATION WITH TAK-003

- Routine vaccination of TAK-003 with catch up covering all eligible children would be associated with a reduction of 34% symptomatic cases and 51% hospitalizations and deaths compared with no vaccination (**Table 1** and **Figure 2**)

TABLE 1: PREDICTED AND AVOIDED NUMBER OF DENGUE CASES. TAK-003 VERSUS NO VACCINATION (TOTAL POPULATION, OVER 20 YEARS)

	No Vaccination	Vaccination With TAK-003	Averted Cases TAK-003 vs No Vaccination
Total infections	2,626,413	2,049,161	577,252 (22%)
Symptomatic cases	808,147	533,703	274,444 (34%)
Hospitalized cases	128,774	63,171	65,603 (51%)
Dengue deaths	76	37	39 (51%)

FIGURE 2: THE PROPORTION OF INFECTIONS AVOIDED BY DISEASE SEVERITY, WITH 95% CIs (TOTAL POPULATION, OVER 20 YEARS)



The proportion of infections avoided (%) are derived from averages.

COST-EFFECTIVENESS OF VACCINATION WITH TAK-003

- From a societal perspective, with discount rates of 3% applied annually, routine vaccination of TAK-003 at 4 years of age with catch up covering all eligible children was dominant over no vaccination, with total cost savings of $408 million and 5314 disability-adjusted life-years averted (**Table 2**)

TABLE 2: COST SAVINGS OF SPECIFIC VACCINATION WITH TAK-003 VERSUS NO VACCINATION (TOTAL POPULATION, OVER 20 YEARS, $154 PER DOSE)

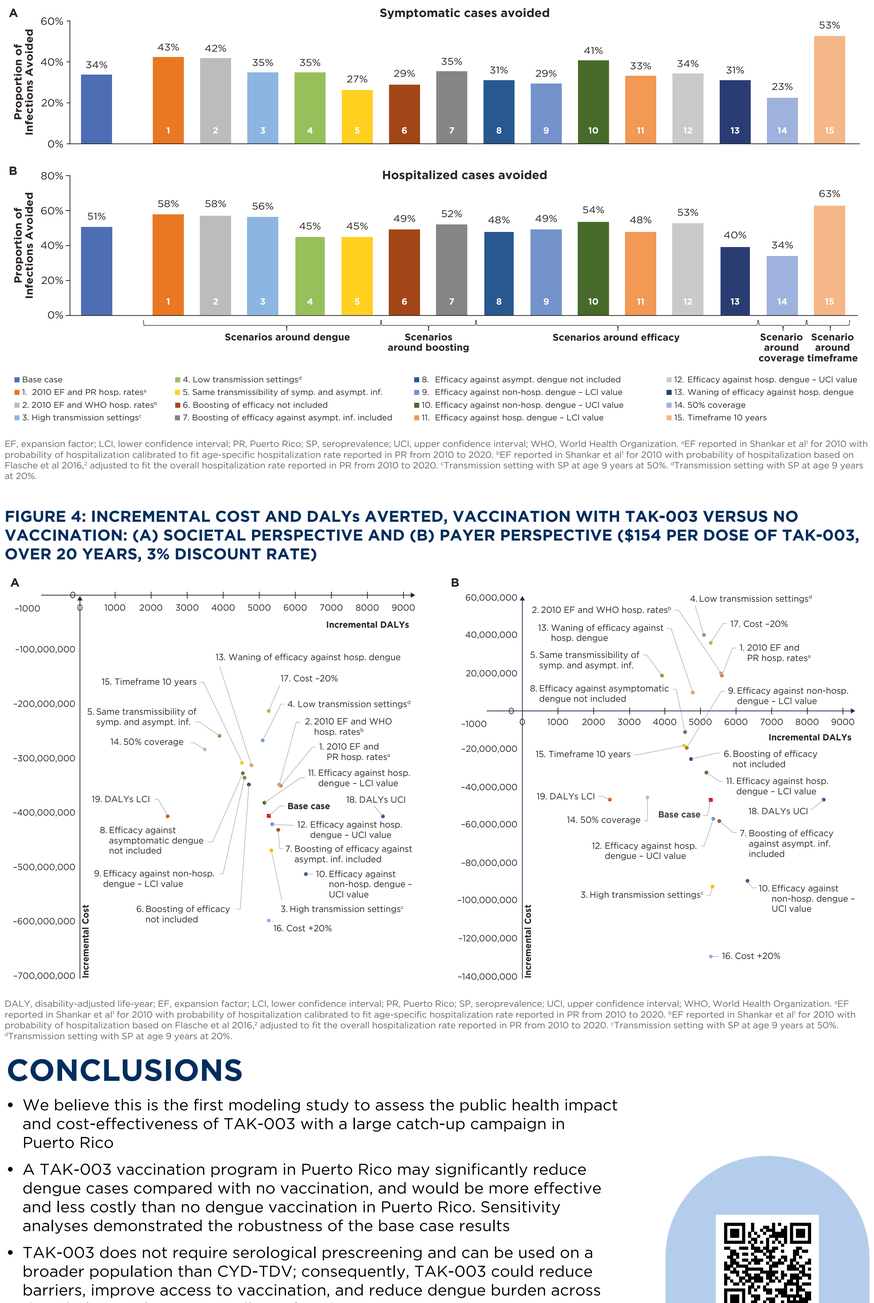
	No Vaccination	Vaccination With TAK-003	Cost Savings TAK-003 vs No Vaccination
DALYs averted	**15,039**	**9725**	**5314**
Societal perspective, total costs	**1,700,426,653**	**1,292,301,241**	**408,125,412**
Direct medical costs	786,832,708	414,296,190	372,536,518
Direct non-medical costs	31,171,222	16,501,320	14,669,902
Indirect costs	882,422,723	536,603,288	345,819,435
Vaccine and administration	0	324,900,443	−324,900,443
Payer perspective, total costs	**786,832,708**	**739,196,633**	**47,636,075**
Direct medical costs	786,832,708	414,296,190	372,536,518
Vaccine-related cost administration	0	324,900,443	−324,900,443

DALY, disability-adjusted life-year.

SENSITIVITY ANALYSIS

- Sensitivity analyses indicated that the base case results were robust to key model parameter variations, as TAK-003 showed considerable benefits in terms of symptomatic and hospitalized cases avoided compared with no vaccination in all scenarios tested (**Figure 3**)
- Sensitivity analyses showed vaccination with TAK-003 vaccine is dominant (i.e., associated with costs saved and quality-adjusted life-years gained) compared with no vaccination from the societal (**Figure 4A**) perspective in all scenarios, and payer (**Figure 4B**) perspective in 9 out of 15 scenarios

FIGURE 3: THE PROPORTION OF INFECTIONS AVOIDED USING VACCINATION WITH TAK-003 VERSUS NO VACCINATION (OVER 20 YEARS, UNDISCOUNTED)



EF, expansion factor; LCI, lower confidence interval; PR, Puerto Rico; SP, seroprevalence; UCI, upper confidence interval; WHO, World Health Organization. [a]EF reported in Shankar et al[1] for 2010 with probability of hospitalization calibrated to fit age-specific hospitalization rate reported in PR from 2010 to 2020. [b]EF reported in Shankar et al[1] for 2010 with probability of hospitalization based on Flasche et al 2016,[2] adjusted to fit the overall hospitalization rate reported in PR from 2010 to 2020. [c]Transmission setting with SP at age 9 years at 50%. [d]Transmission setting with SP at age 9 years at 20%.

FIGURE 4: INCREMENTAL COST AND DALYs AVERTED, VACCINATION WITH TAK-003 VERSUS NO VACCINATION: (A) SOCIETAL PERSPECTIVE AND (B) PAYER PERSPECTIVE ($154 PER DOSE OF TAK-003, OVER 20 YEARS, 3% DISCOUNT RATE)

DALY, disability-adjusted life-year; EF, expansion factor; LCI, lower confidence interval; PR, Puerto Rico; SP, seroprevalence; UCI, upper confidence interval; WHO, World Health Organization. [a]EF reported in Shankar et al[1] for 2010 with probability of hospitalization calibrated to fit age-specific hospitalization rate reported in PR from 2010 to 2020. [b]EF reported in Shankar et al[1] for 2010 with probability of hospitalization based on Flasche et al 2016,[2] adjusted to fit the overall hospitalization rate reported in PR from 2010 to 2020. [c]Transmission setting with SP at age 9 years at 50%. [d]Transmission setting with SP at age 9 years at 20%.

CONCLUSIONS

- We believe this is the first modeling study to assess the public health impact and cost-effectiveness of TAK-003 with a large catch-up campaign in Puerto Rico
- A TAK-003 vaccination program in Puerto Rico may significantly reduce dengue cases compared with no vaccination, and would be more effective and less costly than no dengue vaccination in Puerto Rico. Sensitivity analyses demonstrated the robustness of the base case results
- TAK-003 does not require serological prescreening and can be used on a broader population than CYD-TDV; consequently, TAK-003 could reduce barriers, improve access to vaccination, and reduce dengue burden across the whole population, regardless of serostatus
- The outcome from this study supports the potential implementation of a TAK-003 immunization program in Puerto Rico

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REFERENCES

1. Shankar MB, et al. *PLoS Negl Trop Dis.* 2018;12(8):e0006650.
2. Flasche S, et al. *PLoS Med.* 2016;13(11):e1002181.

DISCLOSURES

JS, RH, SB, MS, VT, RK, DW, and **AR:** employees of Takeda and hold stock/stock options in Takeda. **ZJ, EK,[a]** and **IŻ[2a]:** employees of Putnam. [a]External consultant for Putnam. [b]Employed at Putnam at time of study.

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