Poster EPH55

Validation of a Static Model With a Dynamic Component by Comparing With a Dynamic Model to Assess the Public Health Impact of TAK-003 Vaccination: Case Studies in Thailand and Brazil

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INTRODUCTION

- Dynamic transmission models capture both direct and indirect effects of vaccination; however, they can be complex and computationally demanding
- Static models are easier to use, but do not capture indirect effects and may underestimate vaccine benefit
- A static model with a dynamic component (dyna-static model) was developed to approximate the dynamic model, and used to model the impact of TAK-003 on dengue epidemiology and the design of vaccination programs with TAK-003
- TAK-003 is a tetravalent dengue vaccine based on an attenuated dengue virus (DENV-2) backbone that is licensed for dengue prevention in the European Union, Great Britain, Brazil, Argentina, Thailand, and Indonesia, among other countries[1,2]

OBJECTIVES

- To compare the results of the dyna-static model with the dynamic model and to validate the use of the dyna-static model to assess the impact of TAK-003 vaccination and inform vaccination program design, using 2 distinct dengue-endemic countries as case studies

METHODS

DEVELOPMENT OF THE DYNA-STATIC MODEL

- The dyna-static model is based on a static Markov model with 100 age cohorts (0-99 years) and 16 health states capturing up to 4 consecutive (not serotype specific) dengue infections (**Supplementary Material**) and 3 different levels of severity (asymptomatic, symptomatic nonhospitalized, and symptomatic hospitalized)
- The indirect effect was built into the structure by calculating the number of "infectious units," which combines the number of symptomatic and asymptomatic dengue infections and their relative contributions to transmission (**Figure 1** and **Supplementary Material**)

FIGURE 1: DRIVERS OF THE NUMBER OF INFECTIOUS UNITS

RELATIVE TRANSMISSIBILITY

Vaccination is assumed to turn a certain proportion of symptomatic infections (defined by the VE) into asymptomatic infections[a]; if asymptomatic infections are assumed relatively less transmissible, the number of infectious units is reduced

Two options tested:

1. All infections assumed equally transmissible
2. Symptomatic infections twice as transmissible (preventing symptomatic infections with vaccination will reduce number of infectious units)

EFFICACY AGAINST ASYMPTOMATIC DENGUE

VE against asymptomatic dengue determines the number of asymptomatic infections prevented, reducing the number of infectious units

Two options tested:

1. No VE against asymptomatic dengue
2. Positive VE against asymptomatic dengue equal to half of the VE against symptomatic nonhospitalized dengue

VACCINATION STRATEGY

A higher number of vaccinated individuals increases the magnitude of indirect effects

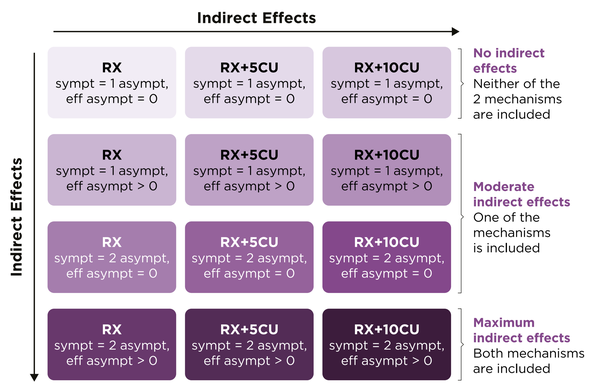
Three options tested:

1. Routine vaccination at X years (RX)
2. Routine vaccination with 5 years of catch-up (RX+5CU)
3. Routine vaccination with 10 years of catch-up (RX+10CU)

RX, routine vaccination at X years old; RX+5CU, routine vaccination with 5 years of catch-up; RX+10CU, routine vaccination with 10 years of catch-up; VE, vaccine efficacy.
[a]The model includes an option where symptomatic infections in vaccinated individuals are completely prevented (rather than becoming asymptomatic). However, this alternative was not used in the current analysis, as it is considered less conservative. Catch-up refers to the one-time vaccination of an additional age cohort in the year of vaccine introduction.

- At each cycle, the number of infectious units is calculated and compared with the reference number of infectious units (without vaccination); this ratio is then used to adjust the probability of infection in subsequent cycles
- The use of "infectious units" allows for incorporation of fluctuating probabilities of infections, which enables the dyna-static model to approximate the dynamic model
- Combining every option for each of the 3 drivers (**Figure 1**) resulted in 12 scenarios with varying magnitudes of indirect effects (**Figure 2**)

FIGURE 2: MAGNITUDE OF INDIRECT EFFECTS FOR EACH OF THE 12 SCENARIOS



asympt, asymptomatic; eff, efficacy; RX, routine vaccination at X years old; RX+5CU, routine vaccination with 5 years of catch-up; RX+10CU, routine vaccination with 10 years of catch-up; sympt, symptomatic.
sympt = 1 asympt: all infections assumed equally transmissible; sympt = 2 asympt: symptomatic infections assumed 2 times more transmissible; eff asympt = 0: no efficacy against asymptomatic dengue; eff asympt > 0: positive efficacy against asymptomatic dengue.
The order of the rows (ie, the contribution of individual mechanisms in the magnitude of indirect effects) will depend on the epidemiology and the specific values of efficacy against asymptomatic dengue. It may also change over time and across vaccination strategies.

MODEL COMPARISON

- The dyna-static model's performance is fine-tuned by varying cycle length and lag time (**Figure 3**)
- The cycle length is defined as the interval at which transitions between health states are evaluated and is considered semiflexible
- Lag time is defined as the number of cycles between a change in infectious units and a corresponding change in the probability of infection

FIGURE 3: ELEVEN COMBINATIONS OF CYCLE AND LAG TIME WERE TESTED FOR EACH OF THE 12 SCENARIOS

	Cycle Length				
No. of Cycles for Lag Time	**1 wk**	**2 wk**	**1 mo**	**2 mo**	**3 mo**
1	1 wk	2 wk	1 mo	2 mo	3 mo
2	2 wk	4 wk	2 mo	4 mo	6 mo
3	3 wk	6 wk	3 mo	6 mo	9 mo
4	4 wk	8 wk	4 mo	8 mo	12 mo
5	5 wk	10 wk	5 mo	10 mo	15 mo
6	6 wk	12 wk	6 mo	12 mo	18 mo
7	7 wk	14 wk	7 mo	14 mo	21 mo
8	8 wk	16 wk	8 mo	16 mo	24 mo
9	9 wk	18 wk	9 mo	18 mo	27 mo
10	10 wk	20 wk	10 mo	20 mo	30 mo
11	11 wk	22 wk	11 mo	22 mo	33 mo
12	12 wk	24 wk	12 mo	24 mo	36 mo

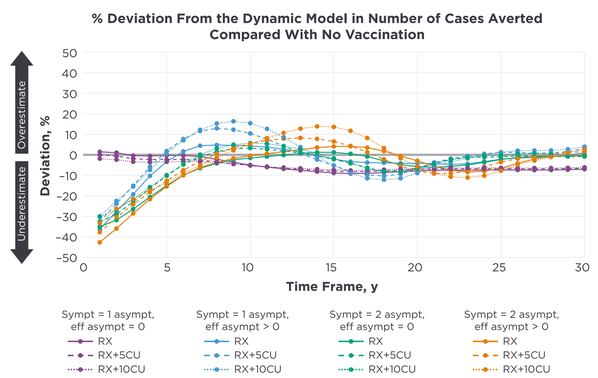
Lag time: Approximately 1 mo; Approximately 2 mo; Approximately 3 mo

- Eleven combinations of cycle length and lag time were tested across 12 scenarios (**Figure 2**), plus 2 no-vaccination scenarios, to find the optimal combination that minimizes deviations between the dyna-static and dynamic models across all assessed outcomes (symptomatic cases, hospitalized cases, and deaths) and for all time frames between 1 and 30 years
- The optimal combination of cycle length and lag time was determined using a set process, as described in the **Supplementary Material**

RESULTS

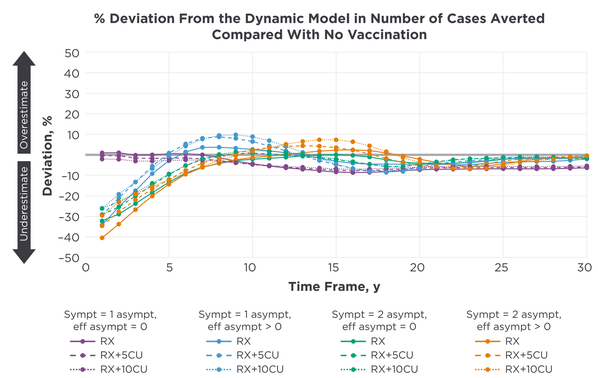
- A cycle length of 2 months and a lag time of 2 months (1 cycle) are considered the optimal combination. Model comparison results are produced using this combination in the dyna-static model
- For both outcomes of symptomatic (**Figures 4** and **6**) and hospitalized (**Figures 5** and **7**) infections, the dyna-static model produces similar results to the dynamic model and in both types of dengue epidemiology
- The magnitude of the dyna-static model's deviations is generally associated with the expected level of indirect effects
- The dyna-static model produces similar results to the dynamic model in both types of dengue epidemiology for time frames longer than ~5-8 years (**Figures 4**, **5**, **6**, and **7**)

FIGURE 4: DYNA-STATIC MODEL VERSUS DYNAMIC MODEL WITH VACCINATION
TOTAL SYMPTOMATIC INFECTIONS: THAILAND



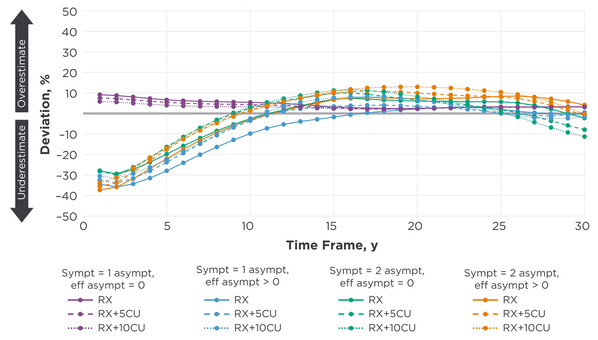
asympt, asymptomatic; eff, efficacy; RX, routine vaccination at X years old (X=8 for Thailand); RX+5CU, routine vaccination with 5 years of catch-up; RX+10CU, routine vaccination with 10 years of catch-up; sympt, symptomatic.

FIGURE 5: DYNA-STATIC MODEL VERSUS DYNAMIC MODEL WITH VACCINATION
TOTAL HOSPITALIZED INFECTIONS: THAILAND



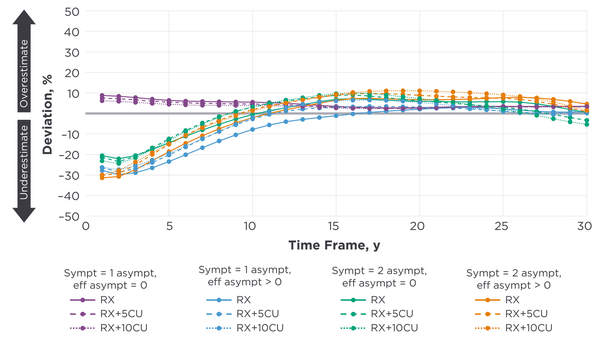
asympt, asymptomatic; eff, efficacy; RX, routine vaccination at X years old (X=8 for Thailand); RX+5CU, routine vaccination with 5 years of catch-up; RX+10CU, routine vaccination with 10 years of catch-up; sympt, symptomatic.

FIGURE 6: DYNA-STATIC MODEL VERSUS DYNAMIC MODEL WITH VACCINATION
TOTAL SYMPTOMATIC INFECTIONS: BRAZIL



asympt, asymptomatic; eff, efficacy; RX, routine vaccination at X years old (X=10 for Brazil); RX+5CU, routine vaccination with 5 years of catch-up; RX+10CU, routine vaccination with 10 years of catch-up; sympt, symptomatic.

FIGURE 7: DYNA-STATIC MODEL VERSUS DYNAMIC MODEL WITH VACCINATION
TOTAL HOSPITALIZED INFECTIONS: BRAZIL



asympt, asymptomatic; eff, efficacy; RX, routine vaccination at X years old (X=10 for Brazil); RX+5CU, routine vaccination with 5 years catch up; RX+10CU, routine vaccination with 10 years catch up; sympt, symptomatic.

LIMITATIONS

- These findings are specific to Thai- and Brazilian-like epidemiological settings and may not be transferable to other types of dengue epidemiology
- The optimal combination of cycle length and lag time was determined by testing all time horizons simultaneously (from 1 to 30 years); the conclusions may change if a local adaptation prioritized a specific time frame (short, medium, or long)
- The dyna-static model performs best when focused on longer timescales and is not well suited for shorter-term predictions (<5 years)

CONCLUSIONS

- We developed a new static model with a dynamic component (dyna-static model) to approximate dynamic dengue transmission to assess the impact of dengue vaccination and inform vaccination program design
- The dyna-static model's validity was tested in 2 distinct dengue-endemic countries across scenarios with different levels of indirect effects; in both case studies, the dyna-static model provided good approximations to the dynamic model over longer-term time horizons (approximately 10 years and longer); long-term validity is key when considering infectious disease dynamics and vaccination impact
- The dyna-static model is a valuable tool for evaluation of dengue vaccines in settings with limited resources and technical capabilities

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REFERENCES

1. Biswal S, et al. *Lancet*. 2020;395(10234):1423-1433.
2. Tricou V, et al. *Lancet*. 2020;395(10234):1434-1443.

DISCLOSURES

EK: External consultant for Putnam. **JS** and **RH:** Employees of Takeda Pharmaceuticals International AG and hold stock/stock options in Takeda Pharmaceuticals International AG. **AT**, **JZ**, and **YGR:** Employees of Putnam. **SA:** Employed at Putnam at time of study. Putnam received funding from Takeda Pharmaceuticals International AG for conducting relevant analysis for this study.

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This poster is intended for healthcare professionals only.