Effectiveness of mass dengue vaccination with CYD-TDV (Dengvaxia®) in the state of Paraná, Brazil: integrating case-cohort and case-control designs

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Summary

Background CYD-TDV (Dengvaxia®) was the first dengue vaccine approved, launched in Brazil in 2015 for individuals aged 9–44 years. We aimed to estimate the effectiveness of CYD-TDV in preventing symptomatic dengue cases during a campaign targeting individuals aged 15–27 years in selected municipalities in Paraná, Brazil. Additionally, we examined whether a history of dengue, as recorded by the surveillance system, modified the vaccine's effectiveness.

Methods We conducted a case-cohort analysis comparing the frequency of vaccination, with at least one dose of CYD-TDV, in individuals with dengue confirmed by RT-PCR, identified by the surveillance system during 2019 and 2020, with the vaccination coverage in the target population. Moreover, in a case-control design using weighted controls, we assessed the documented history of dengue as a modifier of the vaccine's effectiveness. We used a logistic random-effects regression model, with data clustered in municipalities and incorporating covariates such as the incidence of dengue before the campaign, age, and sex. We calculated vaccine effectiveness (VE) as (1-relative risk) x 100%.

Findings 1869 dengue cases were identified, which had a vaccination frequency significantly lower than the overall vaccination coverage in the target population (50.3% vs. 57.2%, respectively; overall VE: 21.3%; 95% confidence interval [CI]: 13.4%–28.4%). In individuals with a documented history of dengue, vaccination had a VE of 71% (95% CI: 58%–80%) in reducing the incidence of dengue. However, vaccination was not associated with a significant reduction in the overall dengue case risk in individuals without a documented history of dengue (VE: 12%; 95% CI: –21% to 36%). In this last stratum, vaccination was associated with reduced cases due to DENV-1 and DENV-4, but an excess of DENV-2 cases.

Interpretation Vaccination led to a significant reduction in reported dengue cases within the target population. The case-control design suggested that this reduction was primarily driven by the benefits observed in individuals with a documented history of dengue. In endemic regions with limited serological testing facilities, a previous history of dengue diagnosis recorded by epidemiological surveillance could be used to triage candidates for CYD-TDV vaccination.

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Research in context

Evidence before this study

When this study was designed, there were two dengue vaccines approved by regulatory agencies to be used on specific populations: the chimeric yellow fever-dengue-tetravalent dengue vaccine (CYD-TDV) and Takeda's tetravalent dengue vaccine candidate (TAK-003). Before CYD-TDV was registered, phase 3 clinical studies were conducted in pediatric patients involving thousands of children, which confirmed that the vaccine's efficacy varies across different serotypes and is influenced by factors such as age and seropositivity. After its registration, few studies have evaluated the safety and effectiveness of the CYD-TDV vaccine.

We searched PubMed for articles published between database inception and August 24, 2023, using the keywords "dengue" AND "vaccine" AND (CYD-TDV OR DENGVAXIA) AND (effectiveness OR impact) AND (cohort OR case-control OR surveillance), with no language restrictions. We identified two observational studies, both following a case-control design, which aimed to estimate the effectiveness of CYD-TDV. The largest study compared 618 RT-qPCR-confirmed dengue cases and 1236 matched controls. These studies did not perform weighting of controls to represent the source population and the results from these studies differed significantly from those seen in clinical trials.

Added value of this study

Our study provides real-world evidence of the effectiveness of CYD-TDV in a large population in Brazil. We found that the vaccine effectively reduced the incidence of dengue in people with a documented history of the disease, providing support for using surveillance data to guide vaccination recommendations in endemic areas.

Additionally, our results confirm the increased risk for DENV-2 cases when the vaccine is administered to individuals lacking prior dengue exposure, validating the clinical trial findings and highlighting the importance of continuous dengue serotype circulation surveillance in endemic areas.

Implications of all the available evidence

As recorded by epidemiological surveillance, clinical history could be used as a criterion for recommending CYD-TDV vaccination, particularly in endemic regions with limited access to serological tests.

Introduction

Dengue viruses are one of the most important arboviruses worldwide, and it is estimated that nearly half of the global population is at risk of infection.[1,2] As no specific treatment is available, intervention efforts for the disease have primarily focused on controlling the vectors that transmit the virus.[3] CYD-TDV (Dengvaxia®) was the first vaccine for dengue to receive regulatory approval and was launched in Brazil in 2015 for individuals aged 9–44 years and administered in three doses with an interval of six months between them.[4,5] It was subsequently recommended by the World Health Organization (WHO) in 2016 for use in populations with a high disease burden, defined as those with a seroprevalence of 70% or greater.[4]

In Southern Brazil, the state of Paraná has experienced outbreaks of dengue since the 1990s. The incidence rate reached 462 cases per 100,000 inhabitants from August 2015 to July 2016.[6] In response, the government of Paraná implemented a vaccine campaign from August 2016 to December 2018 with a target population of 500,000 individuals in 30 municipalities due to the high incidence of the disease, predominantly in the 15 to 27 age group.[6] During the campaign, 302,603 people were vaccinated, with vaccination coverage of 60.5% for at least one dose, 44.2% for two or more doses, and 28.6% for three doses.[7]

In 2017, a retrospective re-analysis of data from three clinical trials,[8–10] employing a novel NS1 assay to determine baseline serostatus, suggested that the vaccine was only effective in protecting individuals previously infected with dengue.[11] Furthermore, the authors reported a statistically significant increase in the risk of hospitalization after 5 years among vaccine recipients who had been dengue seronegative at the time of vaccination (hazard ratio of 1.75, 95% confidence interval [CI]: 1.14–2.70). This new information might have negatively impacted adherence to the full vaccination course. Moreover, the WHO revised its recommendations in 2018 to use a pre-vaccination screening strategy whereby only seropositive persons should be vaccinated.[12]

However, this recommendation may create a barrier to vaccine access, as diagnostic tests to confirm past infection are not widely available. Furthermore, it raises questions about the overall benefit of the mass vaccination campaign and whether using the tools available in surveillance to identify individuals with a history of dengue can aid in identifying those who would benefit the most from the vaccine. In addition, the cross-reactivity between antibody responses to Zika and dengue viruses may further complicate the identification of seropositive individuals in regions where both viruses co-circulate.[13,14]

The present study aimed to estimate the effectiveness of the CYD-TDV vaccine on the incidence of dengue in the individuals vaccinated during the 2016–2018 campaign in Paraná. Additionally, since access to serological tests was limited, we examined whether a history of dengue, as recorded by the surveillance system, modified the vaccine's effectiveness.

Methods

Study design and population

We conducted a case-cohort analysis comparing the frequency of vaccination, with at least one dose of CYD-TDV, in individuals with dengue confirmed by the surveillance system and the vaccination coverage in the target population. Additionally, a case-control design was used to assess whether a documented history of dengue modified the vaccine's effectiveness. This last design made it feasible to collect individual information for controls on characteristics such as history of dengue that is not available for the broader population in the case-cohort study.

The state of Paraná, located in the southern region of Brazil, had 399 municipalities and an estimated population of 11,242,720 inhabitants in 2016. The vaccination campaign targeted individuals aged 15–27 years in 28 municipalities with recent history of recurrent outbreaks. Two other municipalities with an incidence greater than 8000 cases per 100,000 inhabitants in the year preceding the campaign vaccinated individuals aged 9 to 44.[7] For this study, we included only the municipalities that, besides participating in the campaign, reported dengue cases during 2019 and 2020. Furthermore, we limited the study population to individuals 15–27 years old during the campaign, which was the common age group across all the municipalities. Moreover, in the municipalities with the expanded-age vaccinated group, the number of cases identified in groups other than those aged 15–27 was small (12 and 24 cases for those aged 9–14 and 28–44, respectively).

We defined cases of dengue as those confirmed by RT-PCR, reported between Jan 1, 2019, and Dec 31, 2020, in the Notifiable Diseases Information System (*Sistema de Informação de Agravos de Notificação*–Sinan), a national surveillance system, or in the Local Environment Manager (*Gerenciador de Ambiente Local*–GAL), an information system for public health laboratories. This period started more than 30 days after the administration of the last doses in the vaccination campaign. Secondary outcomes included serotype-specific cases and dengue hospitalizations.

In the case-cohort design, we defined a population cohort as a group of individuals aged 15–27 years according to the Brazilian Institute of Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística*–IBGE) projections for each age group, sex (assigned at birth), and participating municipality.[15] The proportion of the exposed cohort for each category was calculated using vaccination records maintained by the government during the campaign.[7]

In the case-control design, two groups of controls were chosen to assess the consistency of the associations.[16] The first group consisted of individuals suspected of having dengue but tested negative (TN) by RT-PCR and other confirmatory tests, such as NS1 antigen and IgM antibody. The second group consisted of individuals reported on Sinan as having other health problems (OHP), including reportable diseases unrelated to dengue: attendance for anti-rabies prophylaxis, exogenous poisoning, and accidents with venomous animals. Cases and controls living in peri-urban or rural areas were excluded from the analysis because they might have limited access to healthcare facilities compared to urban populations, which might have resulted in an increased likelihood of underreporting dengue history. The data obtained from IBGE indicated that 4.3% of the people in the 28 municipalities included in the study lived in rural areas, and only 2.8% of reported dengue cases originated from peri-urban or rural areas.

Data sources

All municipalities participating in the campaign recorded data on vaccinated individuals in a nominal computerized database that included identification (name, sex, and date of birth) and information on administered vaccine doses.

All suspected cases of reportable diseases in the country, treated in the public or private health system, are reported on Sinan, the source for identifying cases and controls. This system includes demographic, clinical, and laboratory data. On demographic data, race/ethnicity is self-reported and based on the categories defined in the Brazilian censo (White, Black, Brown, Asian or Indigenous). Suspected dengue cases were defined as those individuals who lived in or had travelled to an area where dengue transmission was active or the vector was present and who had a fever and at least two of the following symptoms: nausea/vomiting, rash, muscle/joint pain, headache/pain behind the eyes, petechiae/positive tourniquet test result, and low white blood cell count. The surveillance system subsequently classified the reported case based on information from laboratory tests and clinical-epidemiological features.[17]

Case and control information was linked to the individual vaccination database using probabilistic procedures with the OpenRecklink software, version 3.1.824.4086. Independent reviewers implemented seven matching strategies (Supplementary Material, Table S1). The criteria for inclusion as a possible pair in the matching were: concordance of the patient's name and mother's name (above 0.01), year of birth (above 0.74), sex, and municipality (exact). At least two individuals conducted the procedure, and the authors reviewed any disagreements.

Statistical analysis

In the case-cohort design, a database was created to represent the target population in all participating municipalities that had reported dengue cases during the observation period. The database was used to recreate the distribution of inhabitants according to vaccination status, sex, and two age groups (15–20 and 21–27 years) in each of the municipalities. The corresponding value for each pattern of covariates was calculated using the population estimate from IBGE and the count of vaccinated individuals recorded in the campaign database.

The population cohort information did not distinguish between urban, peri-urban, and rural areas because the vaccine database did not include information on the location of residence. However, we observed that the vaccination frequency of both cases and controls in the urban region was similar to those excluded from the rural and peri-urban areas (cases: 50.3% vs. 46.3%, p = 0.58; TN controls: 10.4% vs. 6%, p = 0.18, OHP controls: 48.8% vs. 48.9%, p = 0.97). Based on this, we assumed that the analysed vaccination coverage distribution represents the urban population from which the cases proceeded.

We pre-selected the adjustment variables through a directed acyclic graph (DAG) to estimate vaccine effectiveness. Previous incidence of dengue is thought to affect 'individuals' perception of risk, which can subsequently influence their knowledge, attitudes, and practices, including their interest in vaccinating.[18,19] Additionally, previous incidence can affect the subsequent risk of infection, along with other contextual factors, including the degree of urbanization and any control actions adopted by the municipality. Furthermore, age and sex can affect campaign adherence and the risk of transmission and disease, and age can also be a determinant of previous dengue infections in endemic areas (Fig. 1).

To estimate the effectiveness, we used a random-effects logistic regression model accounting for municipal clustering. In this way, a two-level model was specified to be able to adjust both for the incidence of dengue in the municipality of residence in the year before the campaign (August 1, 2015–July 30, 2016), as a contextual-level determinant, and age and sex, as individual-level covariates.

The case-control design used weighting to ensure the controls accurately reflected the target population's characteristics. The weight assigned to each control corresponded to the inverse probability of being included in the study based on vaccination status, sex, age group (15–20 and 21–27 years), and area of residence. To avoid having too few controls according to covariate patterns, municipalities were grouped into four areas based on proximity (Supplementary Material: Figure S1, Table S2). The estimates were obtained from two-level random-effects logistic models that, in addition to the prior municipality incidence (contextual level), included age as a continuous variable, sex, history of dengue, and an interaction term between vaccination and history of dengue (individual-level covariates). We documented the history of dengue as a record of a probable case of dengue reported on Sinan, with the onset of symptoms between January 2008 and July 2016. The surveillance system defined probable cases as those confirmed by laboratory criteria, those classified by clinical-epidemiological criteria, or inconclusive cases. Besides at least one dose, with the case-control design, we also estimated the effectiveness of three vaccine doses compared with no vaccination. After comparing the cases with each control group, we pooled the

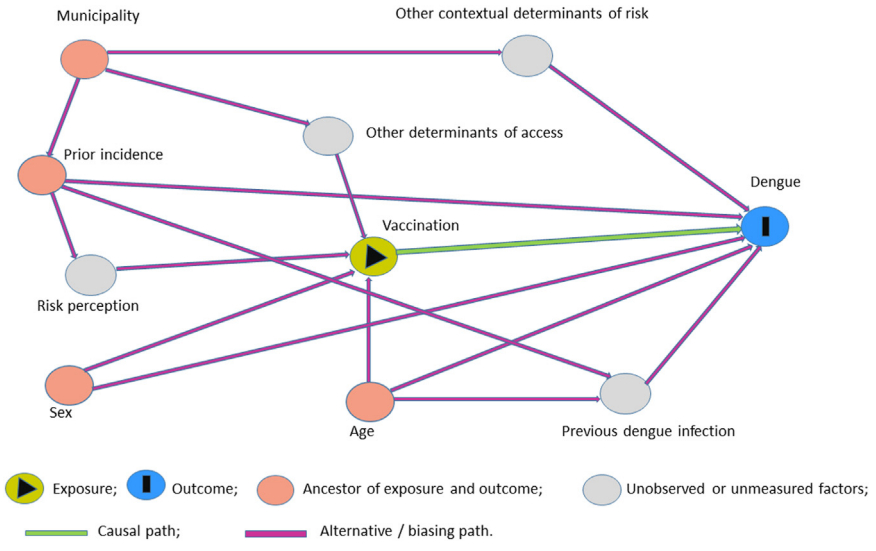


Fig. 1: Directed acyclic graph (DAG) representing the causal relationship between vaccine, symptomatic dengue, and other covariates.

controls, recalculated the weights, and obtained consolidated estimates.

Because the population cohort and weighted controls aimed to reflect baseline vaccination coverage, odds ratios (ORs) comparing case exposure odds to the reference exposure odds are equivalent to relative risk (RR) estimates.[20–23] Therefore, following the recommendation of Labrecque et al.,[23] we reported these association measures as RRs in this paper. The term "OR" was used only to refer to some estimates comparing cases with unweighted controls. We also calculated vaccine effectiveness (VE) as (1-RR) x 100%.

For interpretation purposes, we consider that people with a documented history of dengue could be representative of the seropositive population. However, the effects observed in people without a documented history of dengue would be mixing the vaccine effects in seronegative and undiagnosed seropositive people. Therefore, we performed a sensitive analysis to calculate probable measures of association in seronegative people, considering two feasible seroprevalences in people without a documented history of dengue: 30% and 40%.[24] Methodological details and results of this sensitivity analysis are presented in the Supplementary Material. The statistical analyses were performed using STATA 17.0 (StataCorp, College Station, Texas, USA).

This study was approved by the Research Ethics Committee of the Federal University of Paraná (Number 2,308,662), which exempted us from asking for informed consent for being based on secondary data.

Role of the funding source

Sanofi contributed to the discussion of the findings, participated in the review of the initial draft, and offered valuable suggestions. However, the authors maintained complete autonomy and held the ultimate responsibility for data analysis, result interpretation, and the submission of the manuscript for publication. In adherence to principles of academic integrity, the authors maintain that they had the unequivocal right to publish their research, irrespective of any disagreement with Sanofi's comments.

It is also pertinent to note that Sanofi did not provide editorial assistance to the manuscript. The authors were solely responsible for the conception, writing, and submission of the paper, as well as subsequent revisions. This declaration underscores the authors' commitment to transparency and the independent development of the research presented in this paper.

Results

Case-cohort design

From Jan 1, 2019, to Dec 31, 2020, 1869 dengue cases were identified in individuals residing in urban areas aged 15–27 years in 28 municipalities that participated in the campaign. When comparing the cases with the target population in these municipalities, we observed a similar distribution of age groups but a slight difference in sex distribution. The likelihood of being vaccinated for dengue cases was significantly lower than that of the population (50.3% [941/1869] vs. 57.2% [252,820/441,945], respectively; Table 1), as evidenced by a crude RR of 0.76 (95% confidence interval [CI]: 0.69–0.83; $p < 0.001$). This measure was 0.79 (95% CI: 0.72–0.87) when adjusted for sex, age group, and previous incidence of dengue in the two-level multiple model (Table 2).

Vaccination was associated with a significant reduction in the incidence of dengue caused by serotype 1 (aRR 0.57; 95% CI: 0.48–0.68). However, no significant association was found between vaccination and cases caused by serotype 2 (aRR 1.08; 95% CI: 0.95–1.22). For serotype 4, we restricted the statistical analysis to two neighbouring municipalities, Foz do Iguaçu and Santa Terezinha do Itaipu, where 130 out of 131 cases were identified. Vaccination was associated with an 87% decrease in the incidence of DENV-4 (aRR: 0.13; 95% CI: 0.07–0.23). No cases of serotype 3 were identified during the study period. There was no significant association between vaccination and the total number of hospitalizations for dengue (Table 2).

Variable	Cases (n = 1869)	Population cohort (n = 441,945)[a]
Sex—n (%)		
Female	1000 (53.5)	222,356 (50.3)
Male	869 (46.5)	219,589 (49.7)
Age group		
15–20 years old	876 (46.9)	202,076 (45.7)
21–27 years old	993 (53.1)	239,869 (54.3)
Vaccinated	941 (50.3)	252,820 (57.2)

[a]Estimated population of 28 municipalities participating in the campaign that reported cases of dengue from 2019 to 2020.

Table 1: **General description of dengue cases and the target population for vaccination, 28 municipalities, Paraná, 2019–2020.**

Outcome variables	Number of cases	aRR (95% CI)[a]	VE—% (95% CI)	p-value
Total dengue cases	1869	0.79 (0.72–0.87)	21.3 (13.4–28.4)	<0.001
Serotype-specific cases[b]				
DENV-1	576	0.57 (0.48–0.68)	42.7 (31.9–51.7)	<0.001
DENV-2	1162	1.08 (0.95–1.22)	−7.8 (−21.8 to 4.7)	0.23
DENV-4[c]	130	0.13 (0.07–0.23)	87.2 (77.2–92.8)	<0.001
Hospitalizations	100	1.12 (0.74–1.7)	−12.3 (−70 to 25.8)	0.58

[a]aRRs adjusted for previous municipal incidence, age, and sex in a logistic random effects model with data aggregated at the municipal level. [b]No cases of DENV-3 were identified in the study. [c]Serotype 4 was analysed in only two neighbouring municipalities which included 130 of the 131 cases of DENV-4. Therefore, no additional conditioning for municipal variables was applied.

Table 2: **Overall effect of vaccination with at least one dose of CYD-TDV on dengue outcomes, in 28 municipalities of Paraná, 2019–2020.**

Case-control design to assess the vaccine effectiveness modification by documented dengue history

Compared with the cases, both the control groups had similar distributions regarding demographic variables (Table 3). We observed that the unweighted estimates of the association between vaccination and dengue were positive (OR>1). However, weighted estimates were similar to those obtained in the case-cohort design, especially when comparing cases to the OHP control group. The association measures did not change substantially when adjusting for age (available as a quantitative variable only for the case-control design). Furthermore, there was no significant change in the estimate when adjusting for the previous incidence of dengue (Supplementary Material: Table S3).

The effectiveness of vaccination on the primary outcome was modified by documented dengue history, as evidenced by the ratio of aRRs (without/with dengue history). With the TN control group, the ratio of aRRs was 3.71 (95% CI: 2.15–6.39; $p < 0.001$) for at least one dose and 3.86 (95% CI: 2.0–7.10; $p < 0.001$) for three doses. Similarly, with the OHP control group, the ratio of aRRs was 3.40 (95% CI: 2.42–4.79; $p < 0.001$) for at least one dose and 4.11 (95% CI: 2.45–6.88; $p < 0.001$) for three doses. With the pooled control group, the ratio of aRRs was 3.04 (95% CI: 2.13–4.33; $p < 0.001$) for at least one dose and 3.5 (95% CI: 2.15–5.72; $p < 0.001$) for three doses (Tables 4 and 5).

In the stratum with documented history of dengue, receiving at least one dose and the full course of vaccination were both associated with a significant reduction

Variable	Cases (n = 1869)	TN controls (n = 3897)	OHP controls (n = 5565)
Sex (male)—n (%)			
Female	1000 (53.5)	2116 (54.3)	3077 (55.3)
Male	869 (46.5)	1781 (45.7)	2488 (44.7)
Age (years)[a]	23 (20–27)	24 (21–27)	23 (20–27)
Pregnant (female population) (%)[b]	61 (6.1)	149 (7.0)	120 (3.9)
Race/ethnicity (%)			
White	1403 (75.1)	2924 (75.0)	4159 (74.7)
Brown	287 (15.4)	607 (15.6)	245 (4.4)
Black	85 (4.6)	164 (4.2)	46 (0.8)
Asian	18 (1.0)	32 (0.8)	874 (15.7)
Indigenous	5 (0.3)	3 (0.1)	18 (0.3)
Not informed	71 (3.8)	167 (4.3)	223 (4.0)
Education level (%)			
Incomplete primary (<4th grade)	22 (1.2)	31 (0.8)	59 (1.1)
Incomplete primary (≥4th to <8th grade)	157 (8.4)	309 (7.9)	455 (8.2)
Complete primary	325 (17.4)	698 (17.9)	1074 (19.3)
Complete secondary	680 (36.4)	1352 (34.7)	2539 (45.6)
Higher education	130 (7.0)	235 (6.0)	486 (8.7)
Not reported	555 (29.7)	1272 (32.6)	952 (17.1)
Vaccination			
No. of vaccine doses administered (%)			
None	928 (49.7)	3492 (89.6)	2847 (51.2)
1	231 (12.4)	117 (3.0)	654 (11.8)
2	256 (13.7)	104 (2.7)	729 (13.1)
3	454 (24.3)	184 (4.7)	1335 (24.0)
Any previous dengue episode (%)[c]	115 (6.2)	319 (8.2)	360 (6.5)
Number of past dengue diagnoses (%)			
1	109 (5.8)	304 (7.8)	343 (6.2)
≥2	6 (0.3)	15 (0.4)	17 (0.3)
Diagnostic criteria related to dengue history (%)[d]			
Clinical-epidemiological	65 (56.5)	156 (48.9)	140 (38.9)
Laboratory	35 (30.4)	145 (45.5)	198 (55.0)

TN: Tested negative; OHP: other health problems. [a]Median and interquartile range. [b]Denominator relative to the total number of women. [c]Probable cases of dengue reported on Sinan, including cases confirmed by clinical, epidemiological and laboratory criteria, as well as inconclusive cases, with the onset of symptoms between January 2008 and July 2016. [d]The denominator is the number of cases with a documented history of dengue.

Table 3: **Baseline characteristics of cases and controls, 28 municipalities, Paraná, 2019–2020.**

Outcome within the dengue history strata	TN control group			OHP control group			Pooled control group		
	aRR	(95% CI)	VE (%)	aRR	(95% CI)	VE (%)	aRR	(95% CI)	VE (%)
With a documented history of dengue									
Dengue[b]	0.27	(0.17–0.42)	73	0.25	(0.17–0.36)	75	0.29	(0.2–0.42)	71
DENV-1	0.32	(0.16–0.62)	68	0.27	(0.15–0.48)	73	0.34	(0.21–0.57)	66
DENV-2	0.3	(0.16–0.54)	70	0.29	(0.18–0.46)	71	0.32	(0.2–0.5)	68
DENV-4[c]	0	–	100	0	–	100	0	–	100
Hospitalizations[d]	0.15	(0.01–1.5)	85	0.21	(0.19–2.27)	79	0.21	(0.02–2.26)	79
No documented history of dengue									
Dengue[b]	1	(0.63–1.59)	0.2	0.85	(0.65–1.12)	15	0.88	(0.64–1.21)	12
DENV-1	0.67	(0.38–1.18)	33	0.57	(0.44–0.75)	43	0.62	(0.42–0.91)	38
DENV-2	1.48	(1.22–1.82)	−48	1.22	(1.08–13.8)	−22	1.24	(1.06–1.45)	−24
DENV-4[e]	0.13	(0.07–0.24)	87	0.14	(0.08–0.25)	86	0.14	(0.08–0.25)	86
Hospitalizations	1.27	(0.55–2.96)	−27	1.26	(0.64–2.49)	−26	1.24	(0.61–2.52)	−24

TN: Tested negative; OHP: other health problems. aRR, RR adjusted for the previous incidence in the municipality and, unless otherwise specified, for sex and age. VE, vaccine effectiveness (1- aRR). [a]Unless otherwise specified, the measurements were estimated based on a two-level analysis with data aggregated at the municipal level and adjusted for the previous municipal incidence of dengue and the individual's sex and age. [b]For this outcome, estimates of the ratio of aRRs (without/with dengue history) were: 3.71 (95% CI: 2.15–6.39; p < 0.001), with the TN control group; 3.40 (95% CI: 2.42–4.79; p < 0.001), with the OHP control group; and, 3.04 (95% CI: 2.13–4.33; p < 0.001), with the pooled control group. [c]In the group with a documented history of dengue, the RR was equal to zero because none of the 12 cases of DENV-4 was vaccinated, which prevented obtaining adjusted estimates (as non-vaccination perfectly predicts the event). The Cornfield exact 95% confidence intervals for the ORs were: 0–3.99, with TN controls; 0–0.4, with OHP controls; and, 0–1.05, with pooled controls. Since this estimate was restricted to two contiguous municipalities (Foz do Iguaçu and Santa Terezinha do Itaipu), where 99% of the cases of DENV-4 occurred, we considered it adjusted for previous incidence in the municipality (but not for sex and age). [d]There were four hospitalizations among individuals with a documented history of dengue (1 vaccinated and 3 unvaccinated). [e]In the category without a documented history of dengue, this estimation was restricted to two contiguous municipalities (Foz do Iguaçu and Santa Terezinha do Itaipu), where 99% of the cases of DENV-4 occurred (exempting the need for a multilevel analysis or adjustment for the previous municipal incidence).

Table 4: **Association between of vaccination with at least one dose and dengue cases by dengue history and type of control[a], 28 municipalities, Paraná, 2019–2020.**

Outcome within the dengue history strata	TN control group			OHP control group			Pooled control group		
	aRR	(95% CI)	VE (%)	aRR	(95% CI)	VE (%)	aRR	(95% CI)	VE (%)
With a documented history of dengue									
Dengue[b]	0.29	(0.16–0.5)	71	0.22	(0.12–0.39)	78	0.26	(0.16–0.43)	74
DENV-1	0.21	(0.07–0.64)	79	0.14	(0.05–0.41)	86	0.18	(0.07–0.47)	82
DENV-2	0.33	(0.17–0.63)	67	0.26	(0.13–0.49)	74	0.3	(0.17–0.52)	70
DENV-4[c]	0	–	100	0	–	100	0	–	100
Hospitalizations[d]	–	–	–	–	–	–	–	–	–
No documented history of dengue									
Dengue	1.1	(0.76–1.59)	−10	0.89	(0.68–1.17)	11	0.91	(0.72–1.16)	9
DENV-1	0.62	(0.39–0.99)	38	0.51	(0.39–0.67)	49	0.56	(0.4–0.76)	44
DENV-2	1.65	(1.35–2.01)	−65	1.28	(1.08–1.52)	−28	1.28	(1.13–1.46)	−28
DENV-4[e]	0.23	(0.1–0.54)	77	0.2	(0.09–0.45)	80	0.21	(0.1–0.46)	79
Hospitalizations	1.49	(0.62–3.57)	−49	1.41	(0.65–3.05)	−41	1.38	(0.64–2.96)	−38

TN: Tested negative; OHP: other health problems. aRR, RR adjusted for the previous incidence in the municipality and, unless otherwise specified, for sex and age. VE, vaccine effectiveness (1- aRR). [a]Unless otherwise specified, the measurements were estimated based on a two-level analysis with data aggregated at the municipal level and adjusted for the previous municipal incidence of dengue and the individual's sex and age. [b]For this outcome, estimates of the ratio of aRRs (without/with dengue history) were: 3.86 (95% CI: 2.0–7.10; p < 0.001), with the TN control group; 4.11 (95% CI: 2.45–6.88; p < 0.001), with the OHP control group; and, 3.5 (95% CI: 2.15–5.72; p < 0.001), with the pooled control group. [c]In the group with a documented history of dengue, the RR was equal to zero because none of the 12 cases of DENV-4 was vaccinated, which prevented obtaining adjusted estimates (as non-vaccination perfectly predicts the event). The Cornfield exact 95% CIs for the crude ORs were: 0–11.29, with TN controls; 0–1, with OHP controls; and, 0–2.68, with pooled controls. Since this estimate was restricted to two contiguous municipalities (Foz do Iguaçu and Santa Terezinha do Itaipu), where 99% of the cases of DENV-4 occurred, we considered it adjusted for previous incidence in the municipality (but not for sex and age). [d]Adjusted RR was not estimable for the full course as there were no cases of hospitalization among vaccinated individuals with a history of dengue and only three hospitalizations occurred among unvaccinated. Crude ORs equal to zero and 95% CI were: 0–19.6, with TN controls; 0–1.86, with OHP controls; and, 0–4.4, with pooled controls. [e]In the category without a documented history of dengue, this estimation was restricted to two contiguous municipalities (Foz do Iguaçu and Santa Terezinha do Itaipu), with 99% of the cases of DENV-4 (exempting the need for a multilevel analysis or adjustment for the previous municipal incidence).

Table 5: **Association between of vaccination with the complete course (3 doses) and dengue cases by dengue history and type of control[a], 28 municipalities, Paraná, 2019–2020.**

of the primary outcome (total dengue cases), as well as cases of DENV-1 and DENV-2, in the analyses conducted with both control groups (Tables 4 and 5). Thus, the VE of the partial and complete vaccination courses was over 70% for total dengue cases and higher than 60% for the specific serotypes DENV-1 and DENV-2. As there were only 12 cases of DENV-4 with a documented history of dengue, none of which occurred in vaccinated individuals, the RR was equal to zero (VE = 100%), and a properly adjusted estimate could not be obtained (as non-vaccination perfectly predicted the event). Additionally, although statistically non-significant, the vaccinated population had a lower incidence of hospitalizations than the non-vaccinated in the stratum with a documented history of dengue (Tables 4 and 5).

For individuals without documented history of dengue, vaccination, either at least one dose or the full course, was not significantly associated with the primary outcome. Substantial variations were observed in the association measures according to serotypes. Specifically, vaccination was associated with a significant reduction of DENV-1 cases for at least one dose with the OHP and pooled group (VE: 43% and 38%, respectively; Table 4) and for the three-dose regimen with all control groups (VE of 38%, 49%, and 44% with the TN, OHP and pooled control groups, respectively; Table 5).

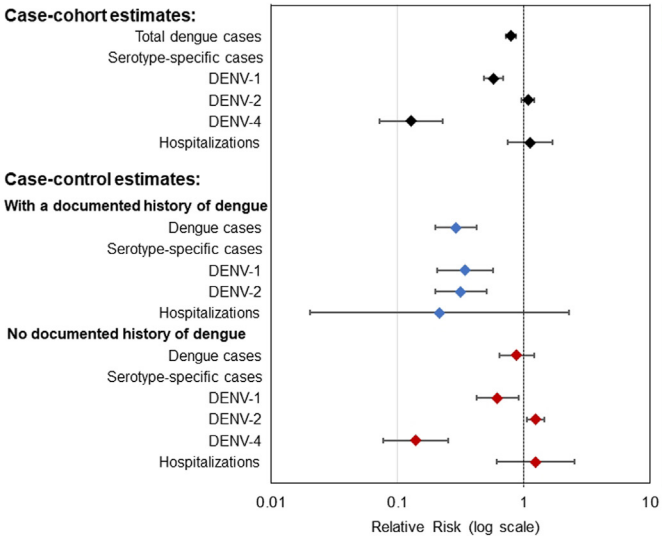
For DENV-2, all comparisons indicated a statistically significant increase in risk with both regimens in the stratum without a documented history of dengue. For DENV-4, a protective association was observed, and effectiveness was more than 70% for both the at-least-one-dose and full vaccination courses. In this stratum, no significant association occurred between any vaccination regimen and hospitalization for dengue (Tables 4 and 5).

According to the sensitivity analysis, the probable RRs for the primary outcome in the seronegative population would be between 1.23 (95% CI: 0.76–1.98) and 1.46 (95% CI: 0.81–2.64), not significantly different from the null value. By serotype, those vaccinated would have a non-statistically significantly lower risk of DENV-1 than those unvaccinated. However, the RR for DENV-2 would reach 2.14 (95% CI: 1.59–2.88) and 3.02 (95% CI: 1.82–5.01) assuming seroprevalences of 30% and 40%, respectively (Supplementary Material: Table S4).

Discussion

We employed a case-cohort design to estimate the effectiveness of dengue vaccination with at least one dose of CYD-TDV during a campaign in an endemic population in Brazil. Our findings indicated that vaccination was associated with a 21% reduction in dengue cases in the 15–27 age group across the 28 municipalities in the state of Paraná that participated in the campaign in 2016–2018 and reported dengue cases in 2019 and 2020. Furthermore, the case-control design suggested that vaccination's impact at the population level was primarily driven by a reduction in cases among individuals who had previously been exposed to the disease (Fig. 2). These results align with those observed in controlled clinical trials, where the protective effect of vaccination was only evident among individuals with serological evidence of previous infection.[11]

We estimated the effectiveness of CYD-TDV (Dengvaxia®) in preventing symptomatic dengue cases during a campaign targeting individuals aged 15–27 years in selected municipalities in Paraná, Brazil.



Study design and key findings

In a case-cohort study comparing vaccination frequency among confirmed dengue cases to vaccination coverage in the target population, at least one dose of CYD-TDV demonstrated a 21.3% vaccine effectiveness (VE) in reducing dengue cases (95% confidence interval [CI]: 13.4% to 28.4%).

In a case-control design, using weighted controls, we estimated that vaccination was effective (VE: 71%; 95% CI: 58% to 80%) in individuals with a documented history of dengue, while it did not significantly reduce the dengue risk in those without such history.

However, in the latter group, vaccination was associated with a reduction in cases due to DENV-1 and DENV-4, but an increase in DENV-2 cases.

Fig. 2: Graphical abstract.

Conversely, vaccination did not demonstrate a significant advantage in preventing the primary outcome among individuals without a prior documented history of symptomatic dengue. While vaccination was found to be associated with a decrease in cases of DENV-1 and DENV-4, it was associated with an excess of DENV-2 cases in this group. It may be because the vaccine induces immunopotentiation mechanisms that specifically increase the pathogenicity of the DENV-2 serotype, as previously reported.[11,25–27] Therefore, although the findings highlight that the population benefit outweighs the individual risk, the data also concur with the WHO 2018 recommendation that only seropositive persons should receive the vaccine. However, following this recommendation implies a need for a pre-vaccination screening strategy, which is not always feasible in endemic areas.[28,29]

This study was based on dengue cases detected through the surveillance system. This characteristic has some implications for the interpretation of the results. It is understood that the reported cases are just a proportion of the total symptomatic dengue cases. The expansion factor (EF), i.e., the value by which the reported cases should be multiplied to estimate the total caseload, appears to be affected by various determinants. EF can vary widely between populations and depending on the epidemiological situation (endemic vs. epidemic).[30,31] Furthermore, dengue severity is recognized as a key determinant of underreporting.[31,32] For instance, in Belo Horizonte (Southeastern Brazil), an EF of 1.6 (95% CI 1.4–1.8) has been estimated for hospitalized cases,[33] while EF values of 5 or greater have been suggested for outpatient cases.[34] Underreporting of symptomatic cases may be due to failure to seek medical attention or misdiagnosis, or also because some facilities, overloaded with cases and understaffed, may neglect the notification of diagnosed cases or report only the more severe. Consequently, our study did not determine the vaccine's effect on the overall number of dengue cases occurring in the community. Instead, our research specifically assessed the effectiveness of mass vaccination on cases identified by the surveillance system, accounting for transmission and serotype circulation during the study period. Despite this limitation, we find the results highly relevant for public health, as the reported cases constitute the majority of primary care burden and typically involve the most severe instances.[35]

Another implication of relying on surveillance data is the necessity for caution in interpreting dengue history as an effect modifier. Our study revealed a robust protective effect in individuals with prior documented dengue exposure, consistent with the observed benefits in seropositive participants of clinical trials.[11] Regarding analysis by serotypes, the vaccine effects in the 15 to 27-year-old population with a documented dengue history mirror the findings by Sridhar and colleagues,[11] who reported significant reductions in hospitalizations for each serotype attributable to vaccination in a 9 to 16-year-old seropositive group. Besides, although people with a documented history of symptomatic dengue are likely seropositive, the stratum without that history (constituting 93% of cases and controls) cannot be considered representative of seronegative individuals. The absence of a documented dengue history does not exclude underreported symptomatic cases, for the reasons mentioned above, or asymptomatic infections. Consequently, the small non-significant benefit of 12% (comparing cases vs. pooled controls) in the stratum without a documented history of symptomatic dengue may mix vaccine effects within seropositive and seronegative individuals.

In this sense, our sensitivity analysis suggested that in the seronegative population, the risk of DENV-2 could be more than double in vaccinated people than in unvaccinated people, consistent with the estimates obtained by Sridhar and colleagues.[11] In that study, the authors reported hazard ratios of 2.41, for hospitalization due to DENV-2, and 3.21 for severe DENV-2 cases, when vaccination was applied in dengue-seronegative people aged 9–16 years and 2–16 years, respectively.[11] Although those association measures were not statistically significant, their point estimates are quite compatible with our results of probable RRs in the seronegative population. Regarding the vaccine's impact on total dengue cases in seronegative individuals, the sensitivity analysis suggested a probable excess risk of between 23% and 46% (Supplementary Material: Table S4). However, this association would lack statistical significance, possibly due to variations in effectiveness across different serotypes. Notably, the harm linked to the increased risk of DENV-2 in vaccinated seronegative individuals seems to be mitigated, at least partially, by protective effects against other serotypes.

We also found an excess risk of hospitalizations in vaccinated people without a documented history of dengue, especially when we analyzed the complete vaccination course. Still, none of the estimates were statistically significant. However, we identified relatively few hospitalizations, so we could not accurately evaluate this outcome in the strata with and without a documented history of dengue. Therefore, the lack of a vaccine–hospitalization association in those without a documented dengue history does not contradict the aforementioned reanalysis of trial data, which indicated that seronegative individuals exhibited a 75% vaccine-associated increase of the hospitalization hazard over a 5-year follow-up.[11] Moreover, we evaluated approximately the third and fourth year after the first dose. Additional time could likely lead to more hospitalizations, allowing greater power to assess the vaccine effect on that outcome.

Considering the mentioned causes of underreporting, the recorded history of dengue might have been affected by the low sensitivity of the surveillance system for previous events. Nevertheless, it is

noteworthy that using the history of a probable case of dengue can assist in identifying vaccination candidates. This classification method based on epidemiological surveillance is feasible in dengue-endemic regions with limited access to serological testing. Therefore, when available, serological testing can be prioritised for people lacking a documented history of dengue to identify seropositive individuals for whom the CYD-TDV vaccine is currently recommended.

Another important consideration is the variation in circulating serotypes, which interferes with the assessment of effectiveness for all cases. In the present study, there were no cases of DENV-3, but there was a high circulation of DENV-2 against which CYD-TDV has documented lower efficacy.[8,9] Recommendations for CYD-TDV often assume long-term protection,[36] prompting the need for policymakers to account for the potential circulation of any serotype over an extended period. Addressing this complexity requires continuous research anchored in real-world regular surveillance, essential for ongoing vaccine effectiveness assessment and informed policy decisions.

Estimating vaccine effectiveness is challenging due to the difficulty in identifying an appropriate comparison group. Methods to select controls, such as using individuals who have tested negative for the disease or cases of other illnesses, may be prone to biases stemming from patterns of medical consultation and reporting.[37,38] Furthermore, selecting controls drawn from the same family or neighbourhood as the patients raises concerns about similar vaccination exposure, as access to preventive interventions tends to be similar within these groups.[20] This phenomenon may explain the findings of a recent study conducted in the same region as the present research, in which 618 patients with dengue were compared with 1236 controls composed of neighbours and study or work colleagues.[39] The frequency of vaccination with at least one dose was 43.8% for the controls, similar to what was observed in the cases (41.3%), but much lower than that reported for the population in vaccination records (60.5%).[7] Analyses performed in that study did not weight the controls, leading to a high risk that the control group does not accurately reflect the prevalence of vaccination in the source population, which may explain the failure to identify a significant reduction of dengue cases attributable to the vaccine.[39]

In our study, we used official statistics and the vaccination campaign records to recreate a population cohort for comparison purposes. Additionally, we aimed to correct or minimize any selection bias by weighting the controls.[40] As a result, the weighted controls were more representative of the campaign's target population regarding critical variables such as vaccination status, sex, age group, and areas. Furthermore, our analysis incorporated adjustments for relevant covariates to control for confounding, which led to results consistent with the efficacy estimated in clinical trials.[11]

In conclusion, this study demonstrated that mass vaccination with CYD-TDV significantly reduced the incidence of dengue cases reported in the campaign's target population. Additionally, the case-control design suggested that this reduction was primarily driven by the protection conferred to individuals with a previously documented history of dengue. The results presented here support that the clinical history, as recorded by epidemiological surveillance, could serve as a criterion for recommending CYD-TDV vaccination for pre-exposed people, particularly in endemic regions with limited access to serological tests.

Contributors

FADQ designed the study, analysed the data, conceived and conducted the sensitivity analyses, and prepared the first manuscript draft. DSC participated in the conceptualization of the study, funding acquisition, project administration, data curation and validation. SMR participated in the study conception, data analysis and interpretation of results. SES participated in the conceptualisation, formal analysis, validation and interpretation of results. AMM, MCVCR, LS, MCMB and EMCPM participated in the investigation, validation and interpretation of results. GG participated to the data curation and software use. GA and CP contributed the investigation and validation. KRL participated in the conceptualization of the study, funding acquisition, data curation, validation, data analysis and interpretation of results.

All authors provided relevant input for manuscript writing and review and have read and approved the final manuscript. Thus, the authors sufficiently participated in the work which enables each to take public responsibility for appropriate portions of the content. Therefore, they agree to be accountable for all aspects in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data sharing statement

The study's data is open for sharing. All methods details are accessible within this paper. However, for any pertinent methodological questions, feel free to reach out to the corresponding author. Anonymized data on individual participants and the data dictionary will be accessible at the Federal University of Paraná research data repository (https://bdc.c3sl.ufpr.br/handle/123456789/121).

Editor note

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Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2024.100777.

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