# 1 ABSTRACT


**Title**

A Pregnancy Registry to Evaluate the Safety of Dengue Vaccine among Inadvertently Exposed Pregnant Women and their Offsprings (DNG16)

**Report date:** 08 July 2024

**Keywords:** Dengue, Dengue vaccine, CYD-TDV, Dengvaxia®, Pregnancy, Pregnancy outcomes, Safety, Pregnancy registry

**Background and rationale**

As with most live attenuated vaccines, CYD tetravalent dengue vaccine (CYD-TDV) is contraindicated in pregnancy due to a theoretical risk to the fetus. CYD-TDV is also contraindicated during lactation. However, because large-scale dengue immunization programs offered in the State of Paraná (Brazil) included women of childbearing age and many pregnancies are unplanned, inadvertent exposure to CYD-TDV during pregnancy is likely to occur.

As agreed with regulatory authorities, this post-authorization safety study (PASS) was conducted to evaluate the safety of CYD-TDV in pregnant women and their offsprings inadvertently exposed during pregnancy.

**Objectives**

**Primary objective**

To evaluate the safety of CYD-TDV in pregnant women and their offsprings inadvertently exposed during pregnancy or up to 30 days preceding their last menstrual period (LMP) with regards to maternal, pregnancy, birth, neonatal and infant outcomes. Specifically, the frequency/rates of these outcomes were: (i) described, and (ii) compared with population-level background incidence rates prior to the introduction of CYD-TDV immunization (i.e., external unvaccinated comparator).

**Secondary objectives**

To describe: (i) the population of CYD-TDV exposed pregnant women, and (ii) the characteristics of CYD-TDV pregnancy exposure with regards to number of doses (during pregnancy and overall), dose intervals, and trimester of exposure.

**Study design**

This is a pregnancy registry study that utilized active identification and enrollment of a cohort of pregnant women of any age and their offspring who were inadvertently exposed to CYD-TDV during their pregnancy or in the 30 days preceding their LMP. Initially, participant enrollment and data collection were expected to be prospective for outcomes that had not occurred at the time of enrollment, and retrospective for events that had occurred prior to enrollment. However, the COVID-19 pandemic delayed the start of enrollment to March 2022 by which time all study outcomes had occurred and all data collected were retrospective. As such, the study period was

from July 2016 (first availability of Paraná's Immunization Registry) to 27 March 2023 (end of data collection), and participant enrollment was from 11 March 2022 to 27 March 2023 (date of last interview/end of data collection). Data collection utilized a hybrid approach comprised of the use of structured interviews supplemented by medical records review, and the use of government databases of Brazil.

This report describes the results of the analysis performed on the data collected between 11 March 2022 and 27 March 2023 with a data lock point date of 29 September 2023. External data obtained from six government databases were also included in the analysis.

**Setting**

The study population consisted of CYD-TDV exposed pregnant women of any age who were identified using Brazil's national adverse event database (Sistema de Informação do Programa Nacional de Imunização Eventos Adversos Pós-Vacinação [SI-PNI EAPV]) that included cases of CYD-TDV pregnancy exposure even in the absence of an adverse event. The study population included all eligible women exposed to CYD-TDV during their pregnancy or in the 30 days prior to their LMP, and the offsprings from the exposed pregnancies. These CYD-TDV exposed pregnant women resided in one of the 30 municipalities of Paraná State (Brazil), where public vaccination campaigns were offered between 2016 and 2018.

Non-participants included CYD-TDV exposed pregnant women and their offsprings who were either ineligible or did not consent to participate in the study, and the comparator populations included age- and municipality-matched unexposed pregnant women and their offsprings identified using the government databases.

**Participants and study size, including dropouts**

As of 27 March 2023, a total of 208 women whose CYD-TDV pregnancy exposure had been reported to the SI-PNI EAPV database had been contacted to participate in the study. Among them, 61 (29.3%) were found to be ineligible due to "invalid contact information". Of the remaining 147 eligible exposed pregnant women, 104 (70.7%) agreed to participate and 43 (29.3%) refused. Among the 104 participants, 2 (1.9%) withdrew from the study before any data were collected, and 102 (98.1%) completed the study. However, there were 5 participants (4.8%) who were discovered during the analysis to have been incorrectly reported as exposed pregnancies in the SI-PNI EAPV database as they were exposed more than 30-days preceding their LMP (i.e., non-exposed, ineligible pregnancies). These ineligible pregnancies were excluded from the analysis, leaving 97 participants for the analysis of maternal adverse events, complications of pregnancy, labour, delivery, and puerperium, and adverse pregnancy outcomes.

The infant population was comprised of 105 infants as there was one twin pregnancy, 99 of whom were born alive, 5 not born alive, and 1 with an unknown birth status. Among the 99 infants born alive, 2 were withdrawn before any data could be collected as their mothers withdrew their consent, leaving 97 infants (including 2 infants who were incorrectly reported as not born alive [1-year data not available]) who completed the study (98.0%). Five infants were excluded from the analysis as their mothers were exposed more than 30-days preceding their LMP (i.e., non-exposed, ineligible pregnancies), leaving 92 infants in the live-birth population for the analysis of birth, neonatal, and infant adverse events.

## Safety data collection

For the structured questionnaire and medical records, all adverse events (AEs) reported/recorded, regardless of seriousness or relatedness (causal relationship) to CYD-TDV, were collected by the Principal Investigator or delegate(s) and reported to the MAH within an expedited time frame. The AEs reported were recorded in the corresponding section of the electronic clinical report form (eCRF) during the interview (i.e., in real-time). The government databases also contained adverse event data and were kept separate from the other data sources and analyzed at the aggregate level only. As such, individual case reports were not available for AEs/serious AEs (SAEs) identified from the government databases.

## Data management, review, validation, and quality control

Clinical data, defined as all data recorded in the eCRF, were managed by the sponsor's authorized data management representative (e.g., Clinical Research Organization [CRO]). Data pertaining to AEs were automatically transferred to the sponsor's pharmacovigilance (PV) department within 24 hours of data entry. The PV department used these data to create individual case safety reports (ISCR) that were stored in the PV database (AEGIS). Each SAE report was reviewed and approved by the Principal Investigator, whereas reports of non-serious AEs were approved by either the Principal Investigator or delegate(s).

Data monitoring and quality control were systematically applied to detect errors or omissions. Data reviews were performed by the Sponsor and data management CRO representative throughout the course of the study. After integration of all corrections in the clinical data and reconciliation of AE data by clinical data management (CDM) and the Sponsor's PV department, the clinical database was locked and released for statistical analysis.

## Variables

The study exposure was CYD-TDV (Dengvaxia®), a tetravalent live recombinant dengue vaccine containing between 4.5 and 6 $\log_{10}$ $CCID_{50}$ per dose of each of dengue virus 1-4.

The primary endpoints (study outcomes) included all maternal, pregnancy, birth, neonatal and infant adverse events reported (serious and non-serious).

Study data also included the mothers' baseline characteristics (e.g., socio-demographics, relevant medical, vaccination and medication histories, history of previous dengue infection, etc.), the characteristics of the exposed pregnancy and CYD-TDV exposure, and the characteristics of the offsprings.

In addition, the expected background prevalence/rate of study outcomes among unvaccinated pregnant women were estimated using age- and municipality-matched historical cohorts for the 3 years preceding the introduction of CYD-TDV public vaccination campaigns (i.e., 2014, 2015, and 2016 external unvaccinated populations) identified using the SISPRENATAL (Sistema de Informação do Programa de Huminazação no Pré-natal e Nascimento – Brazil's prenatal care database) and SINASC (Sistema de Informação de Nascidos Vivos – Brazil's live birth database) databases when available. As these two de-identified databases did not contain a unique identifier, they could not be record linked to one another. As such, the 2014, 2015, and 2016 comparator populations were identified separately for each database. In addition, estimates of the expected background prevalence/rate of study outcomes in a CYD-TDV unvaccinated population of pregnant

women were also obtained from studies conducted in Brazil either prior to the implementation of the dengue immunization program, or in municipalities where a dengue immunization program was not implemented.

**Statistical analysis**

The baseline characteristics of study participants and the characteristics of the CYD-TDV exposed pregnancy were described and qualitatively compared to those of the age- and municipality-matched comparator populations. The characteristics of the CYD-TDV pregnancy exposure were also described.

To assess the safety of CYD-TDV pregnancy exposure, descriptive analyses were undertaken to summarize the frequency/prevalence/rate and corresponding 95% confidence interval (CI) of maternal, pregnancy, birth, neonatal and infant outcomes, which were qualitatively compared with available outcome frequencies/prevalence/rates for the age- and municipality-matched comparator populations. The safety analyses were undertaken using both a subject-level denominator and an event-level denominator. To better understand the potential contributors to the risk of pregnancy related, birth, neonatal and infant adverse events observed in the study, each outcome/event was stratified according to its major risk factors. In addition, time-to-event analyses were also undertaken using the Kaplan-Meier (KM) method for pregnancy outcomes and preterm birth, outcomes for which the timing of the event could be clinically relevant.

**Results**

**Baseline and pregnancy characteristics**

A total of 97 CYD-TDV exposed pregnant women (participants) and their 92 offsprings (live-birth population) were included in the analysis. The mean (standard deviation [SD]) age of participants at the start of pregnancy was 21.4 (3.75) years, with 34.0% being <20 years of age. Nearly half of participants (48.5%) were either overweight (body mass index (BMI) ≥25 to <30: 32.0%) or obese (BMI >30: 16.5%). Primary school or less was the highest level of education attained by 30.9% of participants, and an additional 62.9% had completed high school. In addition, the majority of participants (83.5%) resided in households of low (monthly household income of ≥1 to <3 minimum wage: 63.9%) or very low income (monthly household income <1 minimum wage: 19.6%).

Among participants who reported their obstetrical history, 70.8% (68/96) reported no previous pregnancy (gravidity = none), indicating that the CYD-TDV exposed pregnancy was their first pregnancy. Similarly, the majority of participants (80.0%, 76/95) reported no previous pregnancy carried ≥20 weeks (parity = none). Nine participants (9.5%, 9/95) reported a previous miscarriage/spontaneous abortion, 1 (1.1%, 1/95) had a previous stillbirth, and 2 (2.1%, 2/95) had a previous premature birth. Preexisting diabetes and hypertension were reported by only 2 (2.1%) and 4 (4.1%) participants, respectively.

Approximately 76.3% of participants (61/80) received at least one vaccine during their pregnancy, primarily a pertussis containing vaccine, followed by influenza and hepatitis B, and 85.4% (70/82) took at least one medication during their pregnancy (primarily iron supplement, followed by folic acid, antibiotic, and vitamin supplement). While most of the CYD-TDV exposed pregnancies were classified as low risk in all trimesters, 10.5% (8/76), 15.3% (11/72) and 19.1% (13/68) were

classified as high risk in the first, second, and third trimester, respectively. On average, participants had 7.2 prenatal care visits, and the mean (SD) gestational age at the first visit was 11.0 (6.66) weeks. All but one of the CYD-TDV exposed pregnancies were singleton pregnancies.

Using the SISPRENATAL database, 964 age- and municipality-matched pregnancies were identified for the comparator populations. A separate comparator population was identified using the SINASC database and included 970 age- and municipality-matched pregnancies and 981 infants owing to pregnancies with multiple fetuses. Both comparator populations were similar to participants with regards to age, municipality of residence, parity, history of a previous stillbirth, ectopic pregnancy, caesarean delivery, preexisting diabetes, and preexisting HIV. However, the comparator population was less likely than participants to be overweight (22.7% vs. 32.0%, respectively) or obese (14.7% vs. 16.5%, respectively), and less likely than participants to have had a previous miscarriage/spontaneous abortion (6.7% [65/964] vs. 9.5% [9/95], respectively). Moreover, the comparator population was less likely than participants to have their pregnancy classified as high-risk in the first (6.1% [59/964] vs. 10.5% [8/76]), in the second (7.4% [71/964] vs. (15.3% [11/72]), and in the third trimester (5.6% [54/964] vs. 19.1% [13/68]). Suggesting that participants may have been at greater risk of some pregnancy related adverse events than the age- and municipality-matched comparator populations.

**Characteristics of CYD-TDV exposure**

The majority of participants (n=83, 85.6%) were exposed to CYD-TDV during their first trimester, while 7 participants each (7.2%) were exposed in their second trimester and preconception period. The median (Q1, Q3) gestational age at pregnancy exposure was 3.7 (2.0, 6.6) weeks. Among the 39 participants who received a dose of CYD-TDV prior to the pregnancy exposure dose, the mean (SD) interval between the 2 doses was 221.6 (82.01) days. One participant received two doses during pregnancy with a dose interval of 180 days.

**Characteristics of CYD-TDV exposed women's offsprings**

The live-birth population was comprised of 92 offsprings born alive who were exposed to CYD-TDV in utero, of whom 54.3% were males. The mean (SD) gestational age at birth was 38.4 (2.08) weeks and 100% of infants for whom head circumference at birth was available had a normal head circumference.

**Maternal Adverse events**

A total of 6 participants (6.2%, 95% CI: 2.87, 12.84) reported 9 adverse events, all non-serious. The two most common adverse events were *Vaccination site pain* (2.1%, 95% CI: 0.57, 7.21) and *Myalgia* (2.1%, 95% CI: 0.57, 7.21).

**Complications of pregnancy, labour, delivery, and puerperium**

The prevalence of gestational hypertension (2.1% [95% CI: 0.57, 7.21] vs. 0.8% [95% CI: 0.42, 1.63] for participants vs. comparator population, respectively), preeclampsia (1.0% [95% CI: 0.18, 5.61] vs. 0.7% [95% CI: 0.35, 1.49]), eclampsia (2.1% [95% CI: 0.57, 7.21] vs. 0.2% [95% CI: 0.06, 0.75]), gestational diabetes (2.1% [95% CI: 0.57, 7.21] vs. 0.3% [95% CI: 0.11, 0.91]), preterm labour (2.1% [95% CI: 0.57, 7.21] vs. 1.2% [95% CI: 0.71, 2.16]), and premature membrane rupture (4.1% [95% CI: 1.62, 10.13] vs. 0.9% [95% CI: 0.49, 1.76]) reported by participants was similar to that identified for the SISPRENATAL comparator population

considering the overlapping confidence intervals. Conversely, the prevalence of urinary tract infection (UTI) (25.8% [95% CI: 18.11, 35.28] vs. 4.4% [95% CI: 3.24, 5.84]) and gestational syphilis (5.2% [95% CI: 2.22, 11.50] vs. 1.0% [95% CI: 0.56, 1.90]) was higher in participants than in the comparator population, and the non-overlapping confidence intervals suggest that these differences were statistically significant. At least 20 out of the 25 participants reporting UTI had one or more risk factor for gestational UTI. Three of the 5 participants reporting gestational syphilis had a risk factor for this infection.

There was no corresponding prevalence data available for the SISPRENATAL comparator population for the following outcomes: gestational anemia (18.6%, 95% CI: 12.07, 27.44), cervical dystocia (10.3%, 95% CI: 5.70, 17.95), oligohydramnios (7.2%, 95% CI: 3.54, 14.15), placenta abruption (3.1%, 95% CI: 1.06, 8.70), toxoplasmosis (3.1%, 95% CI: 1.06, 8.70), chorioamnionitis (1.0%, 95% CI: 0.18, 5.61), breeched presentation at delivery (1.0% (95% CI: 0.18, 5.61). As such, the prevalence of these complications was compared with the expected background prevalence among CYD-TDV unvaccinated pregnant women obtained from studies conducted in Brazil (see Discussion). Except for breeched presentation at delivery, at least 1 participant reporting each outcome had at least 1 risk factor.

Nineteen participants (19.6%, 95% CI: 12.91, 28.58) reported at least one complication of pregnancy classified as “other”, all of which were reported by ≤3 participants. These complications included, lower abdominal pain (n=3), hyperemesis gravidarum (n=3), vaginal hemorrhage (n=3), with all other complications reported by only one participant. In addition, 4 participants (4.1%, 95% CI: 1.62, 10.13) reported at least one complication of labour, delivery, and puerperium classified as “other”.

No events of post-partum hemorrhage or maternal death were identified by participants. None of the complications of pregnancy, labour, delivery, and puerperium reported by participants were assessed as related to CYD-TDV pregnancy exposure.

**Adverse pregnancy outcomes**

Among the 97 participants, 4 pregnancies (4.2%, 95% CI: 1.63, 10.23) ended in a miscarriage/spontaneous abortion; the first event was observed at approximately week 6 of gestation and the last event around week 19 of gestation. At least two participants had at least one risk factor for miscarriage. One participant without a risk factor (1.0%, 95% CI: 0.18, 5.67) reported stillbirth. There were no ectopic pregnancies and induced abortions reported, and the outcome of one pregnancy was unknown.

None of the adverse pregnancy outcomes were assessed as related to CYD-TDV pregnancy exposure.

There was no corresponding comparator data available for the adverse pregnancy outcomes. As such, the rate of these adverse outcomes was compared with the expected background rate among CYD-TDV unvaccinated pregnant women obtained from studies conducted in Brazil (see Discussion).

**Birth outcomes**

Among the 92 infants in the live-birth population, the rate of preterm birth (6.5% [95% CI: 3.02, 13.51] vs. 12.3% [95% CI 10.42, 14.54]) and abnormal (≤7.0) 5-minute APGAR score (1.2%

[95% CI: 0.22, 6.59] vs. 2.4% [95% CI: 1.58, 3.51]) were lower than that observed in the live-birth comparator population; although the overlapping confidence intervals suggest that the differences were not statistically significant. The first event of preterm birth in the live-birth population and live-birth comparator population occurred approximately week 26 and week 22 of gestation, respectively. In both populations, events occurred up to week 36. The rate of small for gestational age (SGA) (9.8% [95% CI: 5.23, 17.56] vs. 10.5% [95% CI: 8.73, 12.57] for the live-birth population and live-birth comparator population, respectively), low birth weight (1500 – 2499 g; 5.4% [95% CI: 2.34, 12.10] vs. 6.4% [95% CI: 5.05, 8.13]) and very low birth weight (<1500 g; 1.1% [95% CI: 0.19, 5.90] vs. 1.1% [95% CI: 0.63, 2.00])) were similar for the live-birth study population and live-birth comparator population. For each outcome, at least one infant had at least one risk factor.

None of the adverse birth outcomes were assessed as related to CYD-TDV pregnancy exposure.

**Neonatal Outcomes**

Among the 92 infants in the live-birth population, 19 infants (20.7%, 95% CI: 13.64, 30.02) had at least one neonatal adverse event. Hypoglycemia, jaundice, and intensive care unit (ICU) admission were the most common neonatal adverse events and were each reported for 6 infants (6.5%, 95% CI: 3.02, 13.51). At least 3 infants who experienced hypoglycemia or jaundice had at least one risk factor. Other neonatal outcomes were reported for ≤2 infants each (pneumonia, respiratory distress syndrome, convulsions/seizures, sepsis, congenital syphilis, hypoxia, bronchiolitis, and other adverse events). No data on neonatal adverse events were available for the live-birth comparator populations. As such, the frequency of each the most common neonatal adverse events reported was compared with the expected background rate among CYD-TDV unvaccinated neonates obtained from studies conducted in Brazil (see Discussion).

None of the neonatal adverse events were assessed as related to CYD-TDV pregnancy exposure.

**Infant Outcomes**

Among the 92 infants in the live-birth population, 15 infants (16.3%, 95% CI: 10.14, 25.17) had at least one infant adverse event. Convulsions/seizures, asthma, and bronchiolitis/bronchitis were most common infant adverse events and were each reported for 2 infants (2.2%, 95% CI: 0.60, 7.58). At least 1 infant had at least one risk factor for asthma and bronchiolitis/bronchitis. Other infant adverse events were reported by 1 infant each (umbilical hernia [congenital abnormality/anomaly], urinary tract infection, etc.). No data on infant adverse events were available for the live-birth comparator populations.

None of the infant adverse events were assessed as related to CYD-TDV pregnancy exposure.

**Discussion**

Study participants and the age- and municipality-matched SISPRENATAL comparator population were similar with regards to most baseline and pregnancy characteristics, but there were nonetheless a greater proportion of study participants who were overweight and obese, had preexisting diabetes, and a previous miscarriage compared with that identified for the comparator population. Participants were also more likely to have had their CYD-TDV exposed pregnancy classified as high risk compared to the comparator population. Moreover, while participants were age-matched to the comparator population, they nevertheless represent a younger subset of the general population

of pregnant women as demonstrated by several studies conducted in Brazil for which the mean age was around 26.0 years and the proportion of women <20 years ranged between 10.5% to 18.1% compared with 34.0% for participants. The latter is not surprising given the young age (15 to 27 years) of the population targeted for dengue immunization in 28 of the 30 municipalities of Paraná where public vaccination campaigns were offered. As such, participants were at higher risk for several study outcomes including gestational UTIs, gestational syphilis, toxoplasmosis, gestational anemia, miscarriage/spontaneous abortion, and preterm labour, while their offsprings were at greater risk of being born prematurely, small for their gestational age, of low birth weight, and with congenital syphilis, or of experiencing hypoxia post-birth. This may explain, in part, why the prevalence/rate of a number of outcomes in participants are numerically higher than that in the comparator populations. Nevertheless, with the exception of gestational UTIs and gestational syphilis, the prevalence of complications of pregnancy, labour, delivery, and puerperium, and the rate of adverse pregnancy and birth outcomes among participants were similar to those identified for the age- and municipality-matched comparator populations for the outcomes that were available in SISPRENATAL and SINASC considering the overlapping confidence intervals. Furthermore, the prevalence of complications of pregnancy, the rate of adverse pregnancy and birth outcomes, and the frequency of neonatal and infant adverse events reported by participants are also similar to those expected from the general population of unvaccinated pregnant women and their offsprings as confirmed by numerous studies conducted in Brazil in the same or similar municipalities as those where a dengue immunization program was implemented but during a time period preceding the implementation of such a program, or conducted in municipalities where such immunization programs had not been implemented.

Gestational UTIs and gestational syphilis were the only complications of pregnancy, labour, delivery, and puerperium for which the prevalence observed in participants appeared to be significantly higher than that identified for the age- and municipality-matched SISPRENATAL comparator population considering the non-overlapping confidence intervals. This could be explained, in part, by the higher risk profile of the study participants as previously described. Moreover, the SISPRENATAL database has been found to underestimate the prevalence of complications occurring during pregnancy (i.e, low sensitivity), suggesting that the differences observed for gestational UTIs and gestational syphilis between study participants and the SISPRENATAL comparator population were likely due to under-ascertainment bias rather than true differences. Indeed, the under-ascertainment of complications of pregnancy in SISPRENATAL may also explain why the estimates of prevalence for the SISPRENATAL comparator population are systematically lower than those for study participants. Furthermore, the prevalence of both these complications reported by participants were similar to estimates obtained from multiple studies conducted in Brazil, thereby providing further evidence that differences observed between study participants and the SISPRENATAL comparator population are due to the poor sensitivity of the SISPRENATAL database for identifying complications of pregnancy, labour, delivery and puerperium.

There were no comparator data available in SISPRENATAL for the following complications of pregnancy, labour, delivery and puerperium: placenta abruption, oligohydramnios, toxoplasmosis, gestational anemia, cervical dystocia, chorioamnionitis, and breeched presentation at delivery. However, the prevalence of these complications in the study population were similar to estimates obtained from studies conducted in Brazil, thereby providing evidence against an association between CYD-TDV pregnancy exposure and an increased risk of the complications of pregnancy,

labour, and delivery. There were no reports of post-partum hemorrhage or maternal death in study participants.

As SISPRENATAL does not capture the outcome of a pregnancy, there were no comparator data available to assess whether the rates of adverse pregnancy outcomes from the study participants is within the range of expected rates for a similar population of unvaccinated pregnant women. However, the rates of miscarriage/spontaneous abortion and stillbirth reported by study participants were similar to estimates retrieved from studies conducted in Brazil as well as similar to estimates of miscarriages/spontaneous abortions and stillbirths obtained from publicly recorded data prior to the implementation of the dengue immunization program for the municipalities from which study participants were recruited. This provides evidence against an association between CYD-TDV pregnancy exposure and an increased risk of the adverse pregnancy outcomes. There were no reports of ectopic pregnancy and induced abortion in the study population.

For all the birth outcomes included in the study (preterm birth, abnormal 5-minute APGAR score, SGA, low and very low birth weight), the rates reported for the live-birth population were not only similar to the SINASC live-birth comparator population, they were also similar to estimates obtained from studies conducted in Brazil, thereby providing consistent evidence against an association between CYD-TDV in utero exposure and an increased risk of adverse birth outcomes.

For both neonatal and infant adverse events, data from the live-birth comparator population were not available. Hypoglycemia, jaundice, and ICU admission were the most commonly reported neonatal adverse events in the live-birth population (reported in 6 infants each). The frequency of these events were similar to data identified from the published literature of studies conducted in Brazil, thereby providing evidence against an association between CYD-TDV in utero exposure and an increased risk of these neonatal adverse events. All other neonatal and infant adverse events were reported for ≤2 infants each and all of them represent common conditions for this age group.

In conclusion, no safety concerns were identified in this population of women inadvertently exposed to CYD-TDV during their pregnancy or up to 30 days prior to their LMP and their offsprings exposed in utero. Nonetheless, as inadvertent CYD-TDV exposure in pregnancy is rare, and the number of events observed in the current study is small, the impact of CYD-TDV pregnancy exposure should continue to be monitored.