NON-INTERVENTIONAL POST AUTHORIZATION SAFETY STUDY (PASS) PROTOCOL

Study Title

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

The Study is conducted by Sanofi Pasteur hereinafter referred also as the Market Authorization Holder ("MAH")

PASS INFORMATION

Protocol version identifier	DNG16 version 5.0, dated 06 Feb 2019
Date of last version of the protocol	DNG16 version 4.0, dated 18 March 2015
WHO Universal Trial Number (UTN)	U1111-1212-3443
Active substances	Contains between 4.5 and 6 log10 Cell Culture Infectious Dose 50% (CCID50) per dose of CYD serotypes 1, 2, 3 and 4
Procedure number	Not applicable
Marketing Authorization Holder	Sanofi Pasteur SA Campus Sanofi Lyon, 14 Espace Henry Vallée F-69007 Lyon, France
Joint PASS	Not applicable
Research question and 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 will be: (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 objective:** To describe the characteristics of CYD-TDV pregnancy exposure with regards to number of doses, dose intervals, and trimester of exposure

Country of study	Brazil
Authors	[redacted]
MAH contact person	TBD

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2 LIST OF ABBREVIATIONS

AE	Adverse event
AEFI	Adverse event following immunization
AESI	Adverse event of special interest
AF	Assent form
BMI	Body Mass Index
CDM	Clinical data management
CI	Confidence Interval
CNS	Cartão nacional de saúde (Individual national health card number)
CONEP	Comissão Nacional de Ética em Pesquisa (Brazil's National Ethics Committee)
CRF	Case report form
CRO	Clinical research organization
CYD-TDV	CYD tetravalent dengue vaccine
DENV 1, 2, 3, 4	Dengue virus serotype 1, 2, 3 and 4
DOB	Date of birth
DoH	Department of Health
EC	Ethics committee
ECD	Estimated conception date
eCRF	Electronic clinical record form
EDC	Electronic data capture
EDD	Estimated date of delivery
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EUROCAT	European Surveillance of Congenital Anomalies
FDA	Food and Drug Administration
GPV	Global Pharmacovigilance
GVP	Good Pharmacovigilance Practices
ICF	Informed consent form
ICSR	Individual case safety report
ISPE	International Society for Pharmacoepidemiology
LMP	Last menstrual period
MAH	Marketing authorization holder

MoH	Ministry of Health
PASS	Post authorization safety study
PBRER	Periodic Benefit-Risk Evaluation Report
PI	Principal Investigator
PV	Pharmacovigilance
RMP	Risk Management Plan
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Steering Committee
SIM	Brazil's national mortality database
SINASC	Sistema de Informação de Nascidos Vivos (Brazil's Live Birth Information System)
SI-PNI EAPV	Sistema de Informação do Programa Nacional de Imunização Eventos Adversos pós-vacinação (Brazil's national database of spontaneous adverse event following immunization)
SISPRENATAL	Sistema de Informação do Programa de Humanização no Pré-natal e Nascimento (Brazil's information system for its Prenatal Care and Birth Program)
SmPC	Summary of Product Characteristics
SP	Sanofi Pasteur
TOPFA	Termination of pregnancy for fetal anomaly following prenatal diagnosis
US FDA	United States Food and Drug Agency
VCD	Virologically confirmed dengue
VPN	Virtual protected network
WHO	World Health Organization

3 RESPONSIBLE PARTIES

3.1 OVERALL RESPONSIBILITY

Sanofi Pasteur has the overall responsibility for the conduct of the study.

3.2 STUDY INVESTIGATORS

The Principal Investigator (PI) is responsible for the conduct of the study, submission of local Ethics Committee (EC) application(s), hiring study personnel as required, and reviewing and approving protocol amendments.

The Study Investigator(s) is/are responsible for supporting the PI in the conduct of the study.

The Study National Coordinator is responsible for coordination of the study at a national level and facilitating access to the required databases.

The list of study investigators and their contact details can be found in Appendix 1.

3.3 ADVISORY COMMITTEE

An Advisory Committee will be established to obtain advice from external experts in pediatrics, obstetrics and gynecology, and/or teratology to: (i) assist with the identification of the adverse events of special interest (AESIs) for this study, (ii) review the safety data from the pregnancy registry (at the end of the study or following the identification of a safety signal, and (iii) ensure that results are interpreted and reported accurately at the stage of study report preparation.

4 ABSTRACT

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

Version 5.0, dated 06 February 2019

[redacted]

Sanofi Pasteur

Rationale and background:

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

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

Research question and 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 will be: (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 will be a Pregnancy Registry Study that utilizes active identification and enrollment of a cohort of pregnant women and their offsprings who were inadvertently exposed to CYD-TDV. The study period will be from July 2016 (first availability of Paraná's Immunization Registry) to July 2022 (end of last follow-up interview for offsprings), and the participant enrollment period will be from July/August 2019* to July 2020. Study data will be retrospective for all outcomes occurring between July 2016 and the start of participant enrollment and prospective for outcomes occurring between the start of participant enrollment and July 2022. Data collection will utilize a hybrid approach comprised of the use of structured interviews supplemented by medical records review (primary data sources), and the use of health and mortality databases (secondary data sources).

* Exact date will depend on timing of local and national EC approvals

Population:
The study population will include eligible CYD-TDV inadvertently exposed pregnant women of any age, and the offsprings from the exposed pregnancies, residing in the 30 municipalities of Paraná (Brazil) where public vaccination campaigns have taken place at the time of their pregnancy exposure and providing signed informed consent. These women will be actively identified using Brazil's national database of spontaneous adverse events following immunization [AEFIs] (SI-PNI-AEPV) and will, therefore, originate from the private and public health care sectors. The study could also be extended to other regions and states of Brazil provided study feasibility criteria are met and approval from the relevant local EC is obtained.

Variables:
The exposure of interest will be CYD-TDV vaccination administered any time during a pregnancy or up to 30 days preceding a woman's LMP. The primary endpoints will include all maternal, pregnancy, birth, neonatal and infant adverse events reported (serious and non-serious). Study data will also include the mothers' baseline characteristics (e.g., socio-demographics, relevant medical, vaccination and medication histories, history of previous dengue infection, etc.). In addition, age-appropriate background incidence rates for study AESIs occurring prior to the introduction of CYD-TDV immunization (i.e., external unvaccinated population comparator) will be obtained from appropriate data sources.

Data Sources:
Seven data sources will be used for this study. Primary data sources will include:

1) *Structured questionnaire:* To be used to ascertain self-reported socio-demographic information, medical history, relevant medication and vaccination histories, use of

recognized teratogenic substances (e.g., alcohol), Zika exposure, maternal adverse events (AEs), pregnancy, birth, neonatal and infant outcomes.

2) *Medical record review* (incl., prenatal care booklet, hospitalizations and primary health care records or other settings where antenatal care took place). To be used to supplement and verify self-reported information.

Secondary data sources will include:

3) *SI-PNI EAPV:* Brazil's national database of spontaneous adverse events following immunization. Since pregnancy exposure is subject to mandatory reporting, even in the absence of an adverse event, this database will be used to identify women in the private and public health care sectors exposed to CYD-TDV during their pregnancy.
4) *SISPRENATAL:* Brazil's national prenatal database that includes information on the first and subsequent antenatal visits and puerperium visits taking place in the public health care sector. This database will be used to supplement and verify pregnancy related outcomes and provide background incidence rates for the safety analysis depending on availability.
5) *Paraná State Immunization registry:* This database captures information on CYD-TDV vaccinations administered during public vaccination campaigns. It will be used to confirm the dates of CYD-TDV vaccinations.
6) *SINASC:* Brazil's national birth registry database to be used to supplement and verify self-reported birth, neonatal and outcomes, and provide background incidence rates for the safety analysis.
7) *SIM:* Brazil's national mortality database providing information on dates and causes of deaths. This database will be used to supplement and verify maternal, neonatal and infant deaths and provide background mortality rates.

Study size:
Ultimately, the sample size for this study will depend on the number of pregnant women who were inadvertently exposed to CYD-TDV and had the pregnancy exposure reported to the SI-PNI AEPV database during the study's enrollment period, as well as by the number of these women or their legal delegate who provide signed informed consent. As such, every effort will be made to recruit all eligible women. As of 19 December 2018, 214 reports of inadvertent pregnancy exposure had been submitted to the SI-PNI-AEPV reporting system. However, this number could increase if additional vaccinations campaigns are offered during the study enrollment period.

Data analysis:
Descriptive analyses will be undertaken to: (i) describe the population of women inadvertently exposed to CYD-TDV during pregnancy, (ii) describe pregnancy exposure with regards to number of doses (during pregnancy and overall), dose intervals, and trimester of exposure, and (iii) summarize the safety data from the pregnancy exposure registry with frequencies of outcomes expressed as absolute risk estimates with corresponding 95% confidence intervals (CIs). The denominator for maternal outcomes will be the total number of exposed pregnant women in the registry, whereas the denominator for pregnancy and birth outcomes will be the number of exposed pregnancies for which the outcomes are known (i.e., excluding losses to follow up and study withdrawals). The calculations of risk for neonatal and infant outcomes will be made by dividing the number of events by the total number of

neonates and infants with and without the outcome. All outcomes will be stratified by reporting status (prospective vs. retrospective), as well as by trimester of exposure, with an additional stratum for periconceptional exposure. Reports of multiple CYD-TDV exposures during a pregnancy will be classified according to the earliest pregnancy exposure.

To assess the safety of CYD-TDV exposure during pregnancy, rates of AEs observed among women and their offsprings enrolled in the pregnancy registry will be compared with available age appropriate background rates of events prior to the availability of CYD-TDV (i.e., external unvaccinated comparator).

Milestones:

See section 6.

5 AMENDMENTS AND UPDATES

All changes to the protocol made after participant enrollment has begun will be recorded in a written amendment that will be signed by the Principal Investigator and by the Sponsor; the signed amendment(s) will be attached to this protocol.

Protocol amendments may require regulatory submission(s) (e.g: IRB/IEC) in accordance with local regulations and approval before actual implementation. The PI is responsible to submit an amendment to the protocol to the IRB/IEC. In some cases, an amendment may require a change to the Informed Consent Form.

6 MILESTONES

Date	Milestone
July 2016	Start of study period and of data availability (i.e., first availability of Paraná's immunization registry & first availability of CYD-TDV in Brazil through private market)
March 2019	Ethics Committee (Comitê de Ética em Pesquisa do Setor de Ciências da Saúde da UFPR) submission and review
July/Aug 2019 *	Start of participant enrollment period: (i) Identification of CYD-TDV exposed pregnant women in SI-PNI-EAPV database; (ii) Contact exposed women to discuss study participation; (iii) Obtain signed ICF/AF; verify study eligibility (iv) Assignment of unique, anonymized study identification number
July/Aug 2019 *	Start of structured interviews for self-reported outcomes (primary data source)
July/Aug 2019 *	Start of medical records review (i.e., primary data source)
July 2020	End of participant enrollment period
July/Aug 2019 *	Start of database record linkages and data abstraction
July 2022	End of last follow up (for offsprings) (i.e., end of structured interviews for self-reported outcomes)
September 2022	End of medical record reviews

December 2022	End of database record linkages and data abstraction
January – March 2023	Data cleaning
April – August 2023	Data analysis
Dec 2023	Final study report

* Exact date will depend on timing of local and national EC approvals

7 RATIONALE AND BACKGROUND

7.1 BACKGROUND

7.1.1 Epidemiology of dengue

Dengue is the most important re-emerging mosquito-borne viral disease worldwide. Caused by any of four Dengue virus serotypes (DENV-1 to DENV-4), it is transmitted by mosquitoes from the genus Aedes. It is estimated that approximately 50% of the population worldwide is at risk of dengue infection (1). While most first infections are asymptomatic, symptomatic infections include a mild, flu-like illness known as dengue fever lasting from 2 to 7 days. In some instances, the condition may progress to a life-threatening form called severe dengue or dengue hemorrhagic fever, characterized by severe bleeding, plasma leakage and/or organ impairment.[1] As such, there is an important public health need to prevent dengue fever.

7.1.2 Dengvaxia vaccine

CYD-TDV is a live attenuated viral vaccine produced via recombinant DNA technology using the replicating engine of the 17D-204 yellow fever vaccine virus with envelope proteins (prM and E) of dengue virus serotypes 1, 2, 3 and 4, cultivated on serum-free Vero cells. It consists of equal parts of chimeric DENV1, DENV2, DENV3 and DENV4. CYD-TDV is the first vaccine licensed for the prevention of dengue, and is marketed by Sanofi Pasteur under the brand name DENGVAXIA.

CYD-TDV was licensed in Brazil on 28 December 2015 and, at that time, was indicated for the prevention of dengue disease caused by DENV1, 2, 3 and 4 in individuals aged 9-45 years living in endemic areas. However, recent data have shown that individuals who are seronegative at the time of first dengue vaccination are at increased risk of hospitalized virologically-confirmed dengue (VCD) and severe VCD.[2] As such, the use of CYD-TDV in Brazil is now indicated in seropositive individuals, and future vaccinations campaigns will use a 'test and vaccinate' strategy to ensure that only seropositive individuals are vaccinated. Like most live attenuated vaccines, CYD-TDV is contraindicated in pregnancy and lactation.

7.1.3 Animal studies/human exposure

7.1.3.1 Animal studies

Several studies have been performed to assess the non-clinical safety and bio-distribution of CYD-TDV. To date, no toxicity, including teratogenicity, linked to the vaccine has been observed in any of these studies.[3] According to animal reproductive toxicology studies, CYD-TDV does not appear to be a risk factor for congenital anomalies or other fetal adverse effects.[4] However, the negative predictive value of such studies for predicting human teratogenicity is, for the most part, uncertain.

7.1.3.2 Human exposure

As with most live attenuated vaccines, CYD-TDV is contraindicated in pregnancy because of a theoretical risk to the fetus. Consequently, no clinical studies have been performed to specifically evaluate the safety of CYD-TDV pregnancy exposure. Indeed, pregnancy has been a strict exclusion criterion in all clinical trials and a negative urine test was required for study inclusion and before each subsequent vaccination. Despite these precautions, a small number of female trial participants were inadvertently exposed during pregnancy; this is not entirely surprising given that, on average, at least 50% of pregnancies are unplanned.[5] Given this, data from 19 clinical trials were recently pooled to evaluate pregnancy and birth outcomes among trial women inadvertently exposed to CYD-TDV during pregnancy.[6] A total of 615 trial participants across 19 trials became pregnant during trial follow-up, 404 of whom had received CYD-TDV and 211 placebo (given the 2:1 randomization). For the pregnancy exposure safety analysis, the pregnancy was considered "exposed" if vaccination occurred during pregnancy or up to 30 days preceding the LMP if the LMP was known, or 44 days before the estimated conception date (ECD) if LMP was unavailable, where ECD was based on gestational age at ultrasound examination. Of the 404 pregnant women who received CYD-TDV during trial follow-up, 58 (14.4%) were classified as "exposed during pregnancy," whereas 30 (14.2%) of 211 in the placebo group were considered "exposed during pregnancy". Exposure to CYD-TDV occurred within a few weeks of LMP in most cases, and within approximately a month following LMP in all cases. The proportion of healthy live births was high and relatively balanced between the two groups (81% and 83% for CYD-TDV and placebo exposed pregnancies, respectively). In addition, 10.3% of CYD-TDV exposed pregnancies resulted in the loss of the fetus, compared with 13.3% of placebo exposed pregnancies. This analysis found no evidence of increased adverse pregnancy or birth outcomes among a small group of clinical trial participants inadvertent exposed to CYD-TDV within a few weeks of conception. While these results are reassuring, this analysis also has notable limitations. First, the sample size was too small to detect an increased risk for most adverse pregnancy outcomes of interest. Second, it is not known whether pregnant women inadvertently exposed to CYD-TDV were comparable to those exposed to placebo as the analysis was conducted in a subset of the randomized population and a comparison of baseline characteristics of the two subgroups was not provided. Finally, the results represent the impact of pregnancy exposure within a few weeks of conception among predominantly adolescents. As such, these results may not be generalizable to pregnancy exposures in a real-world setting, particularly in the context of mass vaccination campaigns.

7.2 RATIONALE

CYD-TDV first reached the private market in Brazil in July 2016. Thereafter, large-scale public immunization programs were implemented in 30 municipalities of Paraná. The first vaccination campaign took place from 13 August to 23 September 2016 and all residents aged 15-27 years in 28 municipalities and aged 9-44 years in the remaining 2 were offered the first dose of the three-dose immunization schedule free of charge. The second campaign, which took place from 03 March to 07 April 2017, offered the second dose to residents having received the first dose, as well as a catch up dose for those not yet vaccinated. The third and fourth campaign occurred in September - October 2017 and in March – June 2018 respectively, to administer the last dose to residents having received the first two doses; no catch up doses were offered during these campaigns. Depending on the city, approximately 50% of the

eligible population received at least one dose of the vaccine during the first two campaigns and 30% during the fourth campaign.

Despite being contraindicated in pregnancy and lactation, inadvertent CYD-TDV exposure occurred in Paraná since: (i) the vaccinated population included women of childbearing age owing to the high risk of dengue infection in this age group, and (ii) similar to other countries, the frequency of unplanned pregnancies is high in Brazil, reaching a high of 66.5% in some suburban areas [7].

Given the occurrence of inadvertent CYD-TDV pregnancy exposures in real-world settings and the limited evidence about the safety of such exposure on the women and their offsprings, the MAH proposed to undertake a pregnancy registry study. As agreed with the regulatory authorities, this Post-Authorization Safety Study (PASS) will be conducted to evaluate the safety of CYD-TDV in pregnant women and their offsprings inadvertently exposed during pregnancy.

8 RESEARCH QUESTION AND OBJECTIVES

8.1 PRIMARY OBJECTIVE

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

8.2 SECONDARY OBJECTIVES

i) To describe the characteristics of women exposed to CYD-TDV during pregnancy or up to 30 days before the LMP.
ii) To describe the characteristics of CYD-TDV pregnancy exposure with regards to the number of doses (during pregnancy and overall), dose intervals, trimester of exposure.

9 RESEARCH METHODS

9.1 STUDY DESIGN

9.1.1 Overview

This will be a Pregnancy Registry Study that utilizes active identification and enrollment of a cohort of pregnant women of any age and their offspring who were inadvertently exposed to CYD-TDV anytime during the pregnancy or in the 30 days preceding their LMP (i.e., periconceptional period). The study data collection period will be from July 2016 (first availability of Paraná's Immunization Registry and of CYD-TDV through the private market) to July 2022 (end of last follow up interview for offsprings), and participant enrollment will be from July/August 2019* to July 2020. As such, study outcomes will be retrospective if occurring between July 2016 and the start of participant enrollment, and prospective for outcomes occurring between the start of participant enrollment and July 2022. Data collection will utilize a hybrid approach comprised of the use of structured interviews supplemented by medical records review (primary data sources), and the use of health and mortality

databases (secondary data sources). Study participation will require receipt of a signed informed consent form (ICF) or Assent form (AF) according to local regulations. CYD-TDV exposed pregnant women will be actively identified and recruited using pregnancy exposures reported to the national spontaneous adverse events following immunization reporting system (SI-PNI EAPV). As such, women included in the pregnancy registry will represent those receiving care in the public and private health care settings at the time of their pregnancy exposure. The start of follow-up for the pregnant women will be the date of first CYD-TDV vaccination during the exposed pregnancy and the date of birth for the offsprings. Study outcomes will include maternal, pregnancy, birth, neonatal and infant AESIs, as well as all other reported AEs. Study data will be collected by the study investigators (or research personnel designated by the investigators) through home visit and/or telephone interviews using a structured questionnaire. Self-reported information will be supplemented and confirmed through contact with the woman's physician or other health care provider (e.g., nurse), use of medical records (e.g., prenatal care booklet, hospital, primary health care unit or other settings where antenatal care was provided), and use of record linkages with existing databases (e.g., SINASC, SIM), subject to availability. In cases of discrepancies between data sources, the medical record will be used as the gold standard for most data, followed by databases. Women will be followed for 42 days after the end of pregnancy, irrespective of the duration of the pregnancy, and their offsprings will be followed for up to 12 months post-birth.

* Exact date will depend on timing of local and national EC approvals

9.1.2 Rationale for study design

The current study is an updated version of DNG16 Version 4.0, dated 18 March 2015 originally proposed in the Risk Management Plan (RMP). The original study consisted of a multi-country, prospective Pregnancy Registry with active recruitment of pregnant women and their offspring inadvertently exposed to CYD-TDV during pregnancy (i.e., exposed cohort) identified and enrolled during an antenatal visit as early as possible during the pregnancy. It was also proposed that a similarly identified cohort of unexposed pregnant women, matched on health centre/clinic, maternal age, pregnancy trimester and estimated date of delivery (EDD), and their offsprings would serve as the comparator group (i.e., unexposed cohort). Using this approach, most of the outcomes/AEs would have been prospectively identified. The study was to be conducted in countries where CYD-TDV was first introduced, including in Latin America (Mexico, Brazil) and Southeast Asia (Philippines, Malaysia). However, a number of unexpected major barriers made the implementation of the original study design not feasible. First, there were no mass vaccination campaigns offered in Malaysia and Mexico, countries where usage was expected to be high, which was an important factor for such a rare exposure (i.e., inadvertent pregnancy exposure). Second, the targeting of children and adolescents in the Philippines (ages 9-14 years) and adolescents and young adults in Brazil (ages 15-27 in 28 of 30 municipalities offering public vaccinations campaigns) resulted in few females of childbearing age being vaccinated and even fewer inadvertently exposed during pregnancy. Finally, the short pre-notifications of pending vaccination campaigns made it impossible to plan and implement such a complex longitudinal study prior to the start of vaccination campaigns.

The non-feasibility of DNG16 as originally proposed led the MAH to re-evaluate the methodology to be used in assessing the safety of inadvertent CYD-TDV exposure

during pregnancy. As no large, public vaccination campaigns are planned in the foreseeable future outside of Brazil, the only option available was to leverage the use of existing population-based health and vital statistics databases in Brazil to identify a cohort of CYD-TDV exposed pregnant women and their offsprings, and compare the frequency/rates of adverse events among these exposed pregnancies with those of population-level estimates of these events among pregnant women of similar ages and their offsprings prior to the availability of CYD-TDV vaccination (i.e., unexposed external comparators representing background incidence).

9.2 SETTING

9.2.1 Population

The *target population* will be pregnant women of any age who received at least one dose of CYD-TDV during pregnancy or up to 30 days preceding LMP and the offsprings resulting from those pregnancies (Figure 1). The 30 day period preceding LMP is used as a conservative definition of exposed pregnancy since recall of LMP is often inaccurate; this definition has also been used in clinical trials to define an "exposed pregnancy". When the LMP is not available, the estimated conception date (ECD) will be based on reported gestational age at ultrasound examination. The *study population* will include eligible CYD-TDV exposed pregnant women, and the offsprings from the exposed pregnancies, residing in the 30 municipalities of Paraná (Brazil) where public vaccination campaigns have taken place at the time of their pregnancy exposure who provide signed informed consent. These women will be actively identified using the SI-PNI-AEPV database and will, therefore, represent women receiving care in the private and public health care sectors.

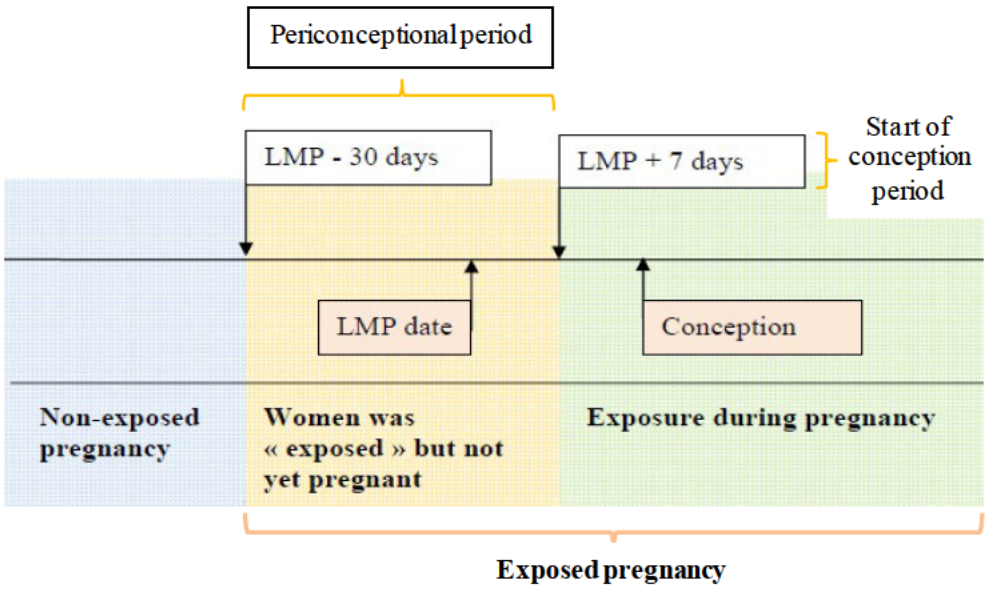

Figure 1. Assessment of CYD-TDV inadvertent pregnancy exposure status

The study could be extended to other regions and States of Brazil provided that: (i) large scale immunization campaigns including women of childbearing age take place, (ii) sufficient notification of such campaigns is received to permit the implementation of this PASS, (iii) individual-level immunization registries are available and linkable

to other data sources, (iv) Ministry of Health (MoH) and Departments of Health (DoHs) are willing to collaborate and provide investigators access to the necessary data and databases, and (v) approval is obtained from the relevant Ethics Committee(s) in accordance with local regulations.

9.2.2 Participant recruitment and follow up

CYD-TDV exposed pregnant women of any age will be actively identified and recruited using the SI-PNI EAPV database. As soon as the study has received Ethics approval from the relevant committees, Paraná's Secretary of Health (Secretaria do Estado da Saúde do Paraná) will extract the list of exposed pregnant women captured in the EAPV database up to that time point; this will assist with study planning as investigators will receive the distribution of potential study participants by municipality/city at the start of the study. This information will be copied to an encrypted and password protected USB pen drive and delivered to the study's Principal Investigator (PI). The exposed pregnant women's nominal data (name, phone number, address, and email) will be extracted from the SI-PNI EAPV database to enable Study Investigators or the research personnel designated by the investigators (hereafter referred to as their "delegate[s]") to contact them or their legal representative if a minor, to describe the study and arrange to obtain the signed ICF/AF from those who agree to participate. The study investigators will be the only persons with access to nominal data. Three attempts will be made to contact potential study participants before considering her "unreachable".

Since the implementation of Parana's dengue immunization programs will precede the study's start of participant enrollment date follow-up and data collection will be retrospective for a large proportion of study participants. However, pregnant women inadvertently exposed to CYD-TDV during vaccinations campaigns implemented either within a few months before or after the start of enrollment will be followed prospectively. For prospectively enrolled women, designated personnel at Paraná's Secretary of Health will query the SI-PNI EAPV database on a bi-monthly basis to identify newly exposed pregnant women. Depending on data availability, the periodicity may be modified.

Participants' date of CYD-TDV immunization will be confirmed through probabilistic linkage (i.e., using nominal data) with the immunization registry; database linkages will be carried out by the DoH or study investigators depending on the availability of qualified personnel. When indicated, a women's self-reported exposure status will be reclassified using the immunization registry as the gold standard. In addition, reports of multiple CYD-TDV exposures during a pregnancy will be classified according to the earliest pregnancy exposure.

Women enrolled in the CYD-TDV pregnancy registry will be followed from the date of their first CYD-TDV vaccination during pregnancy (cohort entry) to up to 42 days following the end of the exposed pregnancy, regardless of the outcome of the pregnancy. The offspring of the exposed pregnancy will be followed for up to 12 months post-birth. In addition, women and offsprings enrolled prospectively (i.e., CYD-TDV exposure either soon before or after study start) will be followed until the earliest of: date of lost to follow-up, withdrawal of consent or death or end of study (July 2022).

9.2.3 Selection of a comparison group

This pregnancy registry study will be a combination of a retrospective (outcomes occurred before the start of participant enrollment) and prospective (outcomes occurred after the start of participant enrollment) cohort study using active identification and enrollment of pregnant women and their offsprings inadvertently exposed to CYD-TDV during pregnancy or up to 30 days preceding the LMP. For reasons described in section 9.1.2, active enrollment of a valid internal comparison group of unexposed pregnant women and their offsprings is not feasible. As such, rates of study AESIs observed among women enrolled in the pregnancy registry and their offsprings will be compared with available background event rates prior to the availability of CYD-TDV for the Brazilian population of similarly aged women and offsprings (i.e., external unexposed comparators) to identify potential safety signals warranting further investigation. Background rates from existing databases (e.g., SISPRENATAL, SINASC, SIM) and other appropriate data sources (e.g., literature) will be used.

9.2.4 Study period

The study pregnancy registry will capture CYD-TDV pregnancy exposures from July 2016 to July 2020 for women (or their legal guardian/representative if a minor) who consent to participate. As such, study outcomes will be retrospective from July 2016 to the start of participant enrollment and prospective if occurring after the start of participant enrollment. The exact start date for participant enrollment will depend on the timing of local and national EC approval but is anticipated for July/August 2019 (to be confirmed).

The study start date of July 2016 corresponds to the start of availability of Paraná's immunization registry and the availability of CYD-TDV through the private sector, while the participant enrollment end date of July 2020 will permit the inclusion of some prospectively followed women and their offsprings *provided* large public vaccination campaigns continue to be offered in Paraná or in other States of Brazil after the start of the study's enrollment period. As previously mentioned, the study could be expanded to other regions of Brazil *provided* the feasibility criteria listed in section 9.2.1 are fulfilled.

9.2.5 Eligibility criteria

9.2.5.1 Inclusion criteria

- CYD-TDV exposed pregnant women of any age residing in the 30 municipalities of Paraná where public vaccination campaigns have been offered at the time of their pregnancy exposure, and whose pregnancy exposure was reported to Brazil's AEFI PV database (SI-PNI AEPV);
- Valid contact information (in SI-PNI AEPV);
- Study participants must provide a signed and dated informed consent form (ICF) or assent form (AF) (based on local regulations), and/or a signed and dated ICF by the parent(s) or other legally acceptable representative (and by an independent witness if required by local regulations) if a minor.*

* Women who meet the inclusion criteria and provide informed consent to participate and complete the structured interview, but who do not consent to medical record review and/or database linkages will still be included in the study; however, their data will be analyzed separately in a sensitivity analysis.

9.2.5.2 Exclusion criteria

- Presence of a major language barrier, medical or psychiatric condition that would prevent a woman from providing informed consent or accurate medical or medication/vaccination histories.

9.2.6 Investigator selection

The study investigators were selected on the basis of their expertise in pediatrics, maternal and child health, epidemiology and clinical research, as well as their expertise with Brazil's public and health databases and their access to these databases (Appendix 1). In addition, these investigators were recommended by Paraná's Secretary of Health.

9.3 VARIABLES

9.3.1 Primary endpoints

The primary study endpoints will include all serious and non-serious maternal, pregnancy related, birth outcomes, neonatal and infant events as described below occurring anytime between cohort entry and the end of follow-up for each event. Although formal diagnostic criteria such as those of the Brighton Collaboration are available for a number of the outcomes of special interest, it is unlikely that these are used in routine clinical practice. As such, the diagnoses will be based on clinician assessment as recorded in the medical record and/or databases.

- ***Maternal adverse events following immunization***: will be defined as all reported adverse events following immunization (serious and non-serious) occurring *independent of the pregnancy* (e.g., injection site reactions, systemic reactions).
- ***Pregnancy related events:*** will be defined as study AESIs (see Appendix 2) and other reported adverse events (serious and non-serious) occurring during the pregnancy, labour and delivery, or the puerperium. Pregnancy related AEs will be classified as: (i) pregnancy outcomes, (ii) complications of pregnancy, and (iii) complications of labour, delivery and puerperium. These outcomes were chosen based on their frequent presentation, their importance as markers of maternal and/or infant health, and their public health relevance. In addition, chorioamnionitis and hypertensive disorders of pregnancy are major risk factors for preterm birth. The definitions used for these outcomes will be consistent with local clinical practice, the European Medicine Agency (EMA) and United States Federal Drug Agency (US FDA) pregnancy guidance documents, and other published pregnancy outcome classification systems such as the European Surveillance of Congenital Anomalies (EUROCAT).
- ***Birth outcomes***: will be defined as study AESIs and other reported adverse events (serious and non-serious) observed or diagnosed at birth. See Appendix 3 for the list of birth outcomes of special interest and their definition.
- ***Neonatal and infant events***: Neonatal events will be defined as study AESIs and other reported adverse events (serious and non-serious) occurring between the day of birth (DOB) and 28 days post-DOB. Study AESIs and other reported adverse events (serious and non-serious) occurring between day 29 and 365 post-birth will be classified as infant events. See Appendix 4 for the list of neonatal and infant events of special interest and their definition.

9.3.2 Data to be collected

In addition to the primary endpoints listed above, the following data will also be collected or derived from collected data:

- Participant unique anonymized identifier (study identification number);
- Relevant maternal baseline characteristics (See Appendix 5 for details);
- Other maternal data: type of conception (e.g., natural, in-vitro fertilization), date of LMP and EDD;
- Characteristics of prenatal care (See Appendix 5 for details);
- Characteristics of CYD-TDV exposure: dates doses administered, number of doses, dose intervals, and timing of pregnancy exposure;
- Offspring data: sex, length, weight, breastfeeding history.

9.4 DATA SOURCES

Seven data sources will be used for this study and these are described below. The primary data sources will include:

(i) *Structured questionnaire:* To be used to ascertain self-reported socio-demographic information, medical history, medication and vaccination histories, use of recognized teratogenic substances (e.g., alcohol), maternal AEs, pregnancy outcomes, neonatal and infant outcomes.

(ii) *Medical record review* (incl., prenatal care booklet, hospitalizations and primary health care records or other settings where antenatal care took place). To be used to supplement and verify self-reported information.

Secondary data sources will include:

(iii) *SI-PNI EAPV:* Brazil's national vaccination spontaneous adverse event following immunization mandatory reporting system database. This database captures cases of pregnancy exposure, even in the absence of an AE, and contains the women's nominal data and CNS. This database will be used to identify pregnant women exposed to CYD-TDV in the private and public health care sectors (i.e., potential study participants) and to obtain contact information for these women.

In Brazil, the SI-PNI AEPV database is administered by the MoH and it is possible to have access to all data for a specific study following a specific request and approval from the appropriate local ethics committee. Data access may be requested via the State Department of Health of Paraná.

(iv) *SISPRENATAL:* Brazil's national, public health care sector longitudinal database created by the MoH. It includes information on the first and subsequent antenatal visits, and puerperium visits taking place in the public health care sector, in addition to information on laboratory tests, ultrasounds and recommended maternal vaccinations. SISPRENATAL captures women's CNS number but not their nominal data. This database will be used to supplement and verify pregnancy related outcomes and provide SAE background rates for the safety analysis depending on availability.

In Brazil, SISPRENATAL is administered by the MoH and it is possible to have access to all the data for a specific study following a specific request and approval from the appropriate local ethics committee. Data access may be requested via the State Department of Health of Paraná.

(v) *Paraná State Immunization registry:* This state-level database captures information on CYD-TDV vaccinations administered during public vaccination campaigns. CNS numbers are not systematically recorded in the registry; hence, data will be retrieved using probabilistic linkage. This database will be used to confirm the dates of CYD-TDV vaccination.

The DoH of Paraná administers this database and it is possible to have access to all data for a specific study following a specific request and approval from the appropriate local ethics committee. Data access is requested via the State Department of Health of Paraná.

(vi) *SINASC:* Brazil's national live birth registry database. This database includes information on some maternal risk factors, delivery conditions, baby's condition at birth and presence of malformations. SINASC will be used to supplement and verify self-reported delivery, birth and neonatal outcomes, and to provide population-level AE background rates (i.e., external unvaccinated comparator data) for the safety analysis.

In Brazil, SINACS is administered by the MoH and it is possible to have access to all data for a specific study following a specific request and approval from the appropriate local ethics committee. Data access may be requested via the State Department of Health of Paraná.

(vii) *SIM:* Brazil's national mortality database. This database captures information on causes of death, as well as maternal and infant demographics. It will be used to supplement and verify maternal, neonatal and infant deaths.

In Brazil, SIM is administered by the MoH and it is possible to have access to all data for a specific study following a specific request and approval from the appropriate local ethics committee. Data access may be requested via the State DoH of Paraná.

9.5 SAMPLE SIZE

Ultimately, the sample size will depend on the number of pregnant women who were inadvertently exposed to CYD-TDV during Paraná's public vaccination campaigns, had this exposure reported to the SI-PNI AEPV database during the study's enrollment period, and provide signed informed consent. As such, every effort will be made to recruit all eligible women. As of 19 December 2018, 214 reports of inadvertent pregnancy exposures had been submitted to the SI-PNI-AEPV reporting system. However, this number could increase if additional vaccinations campaigns are offered during the study enrollment period.

Based on published estimate, adverse pregnancy outcomes such as spontaneous abortions are expected to occur at a frequency of 1/7 (14.3%), low birth weight at 1/12 (8.3%), fetal death/stillbirth at 1/200 (0.5%).[8] Birth defects occur in 1/135 (0.007) pregnancies for genital and urinary tract defects.[9] In Brazil, microencephaly occurs at a frequency ranging from 0.0 to 20.32 per 10,000 live births, depending on

the region.[10] Ultimately, the level of precision (expressed as 95% CI) for the observed point estimates will depend on the number of identified women exposed during pregnancy who consent to participate in the pregnancy registry:

Participation rate	Expected number of exposed pregnancies	Expected observed rate (%)	Number of outcomes	Expected 95% CI
100%	214	14.486%	31	(10.06; 19.93)
		8.411	18	(5.06; 12.97)
		0.467	1	(0.01; 2.58)
75%	160	14.375	23	(9.34; 20.78)
		8.125	13	(4.4; 13.49)
		0.625	1	(0.02; 3.42)
50%	107	14.019	15	(8.06; 22.07)
		8.411	9	(3.92; 15.37)
		0.935	1	(0.02; 5.1)

9.6 DATA MANAGEMENT

9.6.1 Data collection process and schedule

Study investigators or their delegate will collect study data obtained from the structured interviews and the review of medical records; these data will be entered by the investigators or their delegate into an electronic data capture (EDC) system. Record linkages for data extracted from the various study databases will be carried out either by the DoH or the study investigators (depending on availability of qualified personnel) and all study databases will be stripped of nominal data after successful linkage and replaced by the participant's unique, anonymized study identification number.

The primary data collected during the study will be managed using two different platforms depending on whether or not they pertain to an AE. Clinical data, defined as all primary data recorded in the electronic case report form (eCRF), will be managed by the Sponsor's Clinical Data Management (CDM) platform or by authorized representative (e.g., Clinical Research Organization [CRO]). In addition, all data pertaining to AEs that are reported by the Investigators on an individual case safety report (ICSR) form will also be transferred to the Sponsor's Pharmacovigilance (PV) database (AGEIS) managed by the Sponsor's Global Pharmacovigilance (GPV) Department. On the other hand, data extracted from the MoH and DoH's databases will be maintained separately in their original electronic format.

During the study, clinical data recorded in the eCRF will be integrated into the study database under the responsibility of the Sponsor's CDM platform. Data monitoring and quality control in the form of computerized logic and/or consistency checks will be systematically applied to detect errors or omissions. In addition, data reviews may be performed by the Sponsor or representative throughout the course of the study. Questions pertaining to data from primary data sources will be submitted to the investigators or their delegate for resolution using the EDC system. Each step of this process will be monitored through the implementation of individual passwords to

control access to the study database to ensure data integrity. After integration of all corrections in the primary data dataset, and after AE information available from CDM and the GPV Department has been reconciled, the primary data database will be released for statistical analysis. Review of the data from primary data sources is anticipated to take place through the data review process led by Data Management.

For women and offsprings enrolled retrospectively (i.e., outcomes occurred prior to study enrollment), their primary data will be obtained all at once (i.e., one interview) owing to the retrospective nature of the data; however, it may be necessary to contact the mother/legal guardian post-interview for clarification purposes. For women and offsprings enrolled prospectively (i.e., outcomes occurring after enrollment), the data will be collected at pre-specified time points during pregnancy (at enrollment, 1st, 2nd and 3rd trimester). For outcomes in the offsprings, data will be collected within 3 months (±1 month) of birth, then at 6 months (±1 month) and 12th months (±1 month) post-delivery.

Details of the data to be collected and the data collection schedule can be found in Appendix 6.

9.6.2 Participant tracking log

The list of CYD-TDV exposed pregnant women obtained from Paraná's DoH will also serve as the electronic participant tracking log. The following information will be documented in the tracking log: (i) participant unique, anonymized study ID number; (ii) availability of valid contact information (yes/no); (iii) eligibility status (yes/no); (iv) outcome of each contact attempt and contact dates; (v) participation status (yes/no); (vi) reason(s) for non-participation (e.g., unsuccessful contacts, refused, no signed ICF/AF); (vii) follow-up type (prospective/retrospective/both) if applicable (viii) withdrawal status (yes/no) if applicable; (ix) study withdrawal date (if applicable); (x) reason(s) for withdrawal (if applicable); (xi) loss to follow-up status (yes/no), and (xii) date of loss to follow-up (if applicable). This information will be used to prepare the study cohort flow diagram.

To comply with data privacy requirements, data collected on the tracking log will be fully anonymized. As such, the final tracking log will not include any nominal data and study participants will be identified using only their unique, anonymized study identification number.

9.6.3 Procedure for withdrawal of study participants

Women and their offsprings followed prospectively may be lost to follow-up or withdraw from the study, which could introduce bias if the loss is related to the outcome of the pregnancy, birth or offspring. Study investigators or their delegate will make every effort to contact prospectively followed study participants at the pre-specified time points to determine their health status and that of the offsprings. In addition, the relatively short period of follow-up in this study (approximately 18 to 20 months depending on the timing of the reporting of pregnancy exposure) will help to minimize the risk of losses to follow-up, as will obtaining contact information for a close friend/contact not living in the same household as the study participant (i.e., additional source of information for tracking study participants). The impact of losses to follow-up and study withdrawal will also be mitigated by the use of medical records review and linkages with available health and mortality databases to obtain

outcomes data. In this way, outcome ascertainment will be possible even for those lost to follow-up.

9.7 DATA ANALYSIS

The statistical analysis will be conducted under the responsibility of Sanofi Pasteur's Biostatistics platform using SAS® software, version 9.4 or above (SAS Institute, Cary, NC, USA).

9.7.1 Primary analysis

To assess the safety of CYD-TDV exposure during pregnancy, descriptive analyses will be undertaken to summarize the maternal, pregnancy, birth, neonatal and infant outcome data using frequencies expressed as absolute risk estimates with corresponding 95% CIs, and these data will be compared background incidence rates for the age-matched population in Paraná prior to the availability of CYD-TDV (i.e., unvaccinated comparator population). In addition, analyses will be stratified by reporting status (prospective vs. retrospective), as well as by trimester of exposure, with an additional stratum for periconceptional exposure. Reports of multiple CYD-TDV exposures during a pregnancy will be classified according to the earliest pregnancy exposure.

Age-stratified background incidence rates for the outcomes of interest may be publicly available or available from the literature. When needed, background incidence rates for the unvaccinated comparator population (i.e., prior to the availability of CYD-TDV) will be derived from the available health and mortality databases using annual event counts divided by the same year's census data for a population with a similar age distribution as that of the study population.

The number and frequency of outcomes will be stratified into prospective and retrospective, as well as by semester of exposure (earliest date in cases of >1 dose received during the pregnancy), including a stratum for preconception exposure (i.e., LMP - 30 days). The denominator for maternal outcomes will be the total number of exposed pregnant women in the registry, whereas the denominator for pregnancy outcomes will be the number of exposed pregnancies for which the outcomes are known (i.e., excluding losses to follow-up and study withdrawals). The calculations of risk for neonatal and infant outcomes will be made by dividing the number of events observed in the registry for individual outcomes by the total number of neonates and infants with and without the outcome. In addition, rates of AEs observed in CYD-TDV exposed pregnant women and their offsprings will be compared to available background rates of events prior to the availability of CYD-TDV (i.e., external unvaccinated comparator) to determine whether the difference represents a safety signal warranting further investigation.

9.7.2 Secondary analysis

Descriptive analyses will also be undertaken to characterize pregnancy exposure with regards to number of doses received (during the pregnancy and overall), dose intervals, and trimester of exposure (including a stratum for the preconception period), as well as to characterize the population of pregnant women inadvertently exposed to CYD-TDV (see Appendix 5).

9.7.3 Interim analysis

No interim analysis is planned for this registry study as the number of events is expected to be very small given the rarity of these and the small sample size. Nevertheless, some descriptive analyses will be conducted at regular intervals corresponding to the Periodic Benefit-Risk Evaluation Report (PBRER), and included in updates of the risk management plan (RMP) associated with regulatory submissions. The latter analyses will be described in a specific Statistical Analysis Plan (SAP).

9.7.4 Sensitivity analyses

The following sensitivity analyses will be undertaken to test the robustness of the results:

- The primary analysis will be repeated restricted to women receiving care from the public health care sector only as SIPNI/EAPV includes women from both the private and public sector but outcome data for women receiving care in the private sector will be limited to those that are self-reported as the available health and mortality databases reflect care provided in the public sector and the medical records of women in the private sector may not be accessible. Women receiving care from both sectors will be classified as having a private coverage.
- To address the possibility of bias owing to the retrospective nature of some outcomes data, the analysis will be repeated stratified by the nature of the outcomes (i.e., prospective vs. retrospective).
- To address the possibility of misclassification of exposure due to the use of a “30 days prior to the LMP” conservative criteria for the definition of “exposed pregnancy,” the analysis will be repeated excluding pregnancies and offsprings exposed during the preconception period (LMP - 30days) if available data permits.
- To address potential bias introduced by study participants who did not consent to medical chart review and/or database linkages, the analyses will be repeated by excluding these study participants.

9.8 QUALITY CONTROL

This study will be conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE) [Revision 3, 2015], and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide of Methodological Standards, Revision 4, 2015. This will be ensured at an operational technical level by requiring the use of formal procedures for testing and validating all software and databases developed for the project, and by developing early in the project, quality guidelines that affect all work and procedures to be implemented.

Data quality will also be assured through routine monitoring by the Sponsor or delegate, and through periodic cross-checks against the protocol.

9.8.1 Assessment of validity and representativeness of study results

Each data source to be used in this pregnancy registry study has strengths and limitations; therefore, their combined use will leverage their respective strengths and significantly improve overall data quality. For example, the literature suggests that the first antenatal visit is well documented in SISPRENATAL, while subsequent visits

are less complete than that recorded in the prenatal care booklet;[11] therefore, use of both data sources will improve the overall study data quality. Similarly, women's self-reported outcomes will be compared to those recorded in their medical records and the health and mortality databases administered by Brazil's MoH and Paraná's DoH.

For women enrolled retrospectively (i.e., outcomes occurred before study enrollment), study outcomes will be known at the time of data collection, thereby increasing the risk of reporting or recall bias, as well as the risk of ascertainment or detection bias. For example, since CYD-TDV is known to be contraindicated in pregnancy, it is possible that concerned exposed pregnant women would pay closer attention to their health and that of their offsprings. Similarly, physicians and health care providers (HCPs) may undertake more intensive follow-up of exposed pregnant women and their offsprings than of their unexposed counterparts in the general population. Both of these scenarios could result in the detection of more AEs for study participants and their offsprings. It is also conceivable that study participation could be affected by knowledge of outcome status at the time of data collection. For example, exposed pregnant women who experienced a serious complication of pregnancy could be more likely to participate if they wanted to ensure the event was captured and/or reported or, they could be less willing to participate if they were upset or traumatized by the event. Consequently, the direction of the bias resulting from differential participation will be hard to predict in the absence of data on non-participants to assess the presence and direction this source of bias. Moreover, incomplete participation could also affect the generalizability of study results.

As the scenarios described above represent important threats to the validity of the results and to their generalizability, permission will be sought from the Ethics Committee to obtain *aggregate level* information (i.e., anonymized data) on rates of pregnancy, birth, neonatal and infant outcomes of special interest for non-participants, as well as *aggregate level* information on the baseline characteristics and characteristics of prenatal care of non-participants obtained from the MoH and DoH databases to enable a comparison of participants and non-participants, and assess the likelihood, strength and direction of the aforementioned biases. This comparison will also provide an assessment of the representativeness of the pregnancy registry participants.

9.8.2 Data collection, validation and quality control

The Principal Investigator (PI) will be responsible for overall quality assurance at the study site(s).

Study data obtained from the structured interviews and medical record reviews (primary data) will be entered into an electronic case report form (eCRF). Quality control in the form of computerized logic (e.g., to detect "out of range" entries) and/or consistency checks will be systematically applied to detect errors and omissions. In addition, data reviews will be performed by the Sponsor or their delegate (e.g., CRO) over the course of the study. Any questions pertaining to the collected study data will be submitted to the investigator(s) for resolution using the EDC system. Each step of this process will be monitored through implementation of individual passwords to ensure appropriate database access and database integrity.

Review of the data will be through the data review process led by Data Management.

Following the: (i) integration of all corrections in the dataset of primary data, (ii) the reconciliation of AE information available from the CDM and the GPV databases,

and (iii) assessment of the MoH and DoH databases (secondary data) for missing and out-of-range data, the research databases will be released for statistical analysis.

Data extracted from the MoH and DoH existing health and mortality databases (e.g., SISPRENATAL, SINASC, SIM) already exist in an electronic format and will, therefore, not require data entry, nor be included in the EDC system. As such, they will be maintained in their original electronic format as separate databases. However, in order to anonymize these databases prior to analysis, individuals' nominal data will be replaced by their unique study identification number by the study investigators or their delegate(s).

The data collection and validation procedures will be detailed in appropriate operational documents.

9.9 STRENGTHS AND LIMITATIONS OF THE RESEARCH METHODS

The most important strength of this study is that, unlike most pregnancy registries that rely on passive reporting, the identification and enrollment of pregnancy exposures will be active. Another important strength is that self-reported vaccination status and outcomes will be verified using medical record review and database linkages; thereby mitigating the risk of recall and reporting bias, a potential danger with retrospectively collected outcomes. Also, offsprings will be followed for up to 12 months post-birth to assess the risk of birth defects that may not be detected at birth, and to assess the risk of hospitalized and/or severe dengue among infants exposed in utero. On the other hand, this study will also have some limitations that need to be considered. First, the baseline dengue serostatus of most exposed pregnant women will not be known as the vaccinations studied occurred before the recent "test and vaccinate" recommendation. As such, should a safety concern arise, it will not be possible to distinguish between vaccine associated dengue in seronegative vaccinees from vaccine failure or waning immunity in seropositive vaccinees. Second, the majority of outcomes will be ascertained retrospectively, thus increasing the risk of recall and detection bias. However, this risk will be, in part, mitigated by the identification of outcomes using multiple data sources, and by the use of a sensitivity analysis stratified according to the nature of the outcomes (i.e., prospective vs. retrospective) if a sufficient number of women can be prospectively enrolled. Third, women who are unreachable, refuse to participate or have died prior to enrollment may be systematically different from study participants and thus, could introduce bias. However, permission will be sought from the Ethics Committee to obtain *aggregate* level information to undertake a comparison of participants and non-participants with regards to baseline characteristics and characteristics of prenatal care to assess the likelihood, strength and direction of such bias. Fourth, although the identification of CYD-TDV exposed pregnant women will be active, the database used to identify these women (SI-PNI EAPV) is part of Brazil's passive AEFI reporting system. As such, some pregnancy exposures may be missed despite educational efforts to stimulate reporting; however, there is no reason to believe that pregnancy exposures captured in the database will be systematically different from those who may be missed. As such, this will impact the precision of the results but not their validity. Fifth, the use of multiple data sources for identifying outcomes may introduce some discordance; however, the impact of this on outcome misclassification will be minimized by choosing *a priori* a gold standard source for each event. Sixth, given the young age of most vaccinees in Paraná, it is possible that many of the pregnancy exposure will be in adolescents; an age group less likely to carry the pregnancy to

term. The resulting loss of pregnancy, birth, neonatal and infant outcomes will reduce the study's statistical power. Finally, the need for probabilistic linkages may result in some outcomes being missed due to unsuccessful linkages; thereby further reducing the precision of the results (i.e., statistical power). However, in the context that most pregnancy registries use passive surveillance to identify pregnancy exposures, the current study's active, population-based identification and recruitment of CYD-TDV pregnancy exposures should result in a larger sample size than that passively collected.

10 PROTECTION OF HUMAN SUBJECTS

10.1 RESPONSIBILITIES OF THE INVESTIGATORS

The Study Investigators and their delegate(s) will execute the study in accordance with this protocol, applicable local regulations, and international guidelines.

It will be the Study Investigators' responsibility to perform the informed consent procedure with each potential participant prior to enrollment in the study. Study Investigators will also be responsible for conducting the structured interview, completing the eCRF, and recording all data pertinent to the study. However, these activities may be delegated to a qualified and appropriately trained research personnel (e.g., study nurse, medical resident). Study Investigators or their delegate(s) will be responsible for ensuring that the information recorded on the study questionnaire and in the eCRF is precise and accurate.

The Study Investigators or their delegate(s) will fully inform the potential study participant(s), and/or the parent(s) /guardian(s) in the case of a minor, of all pertinent aspects of the study, including the written approval/favourable opinion of the Ethics Committee(s). All participants will be informed to the fullest extent possible about the study in a language and using terms they are able to understand.

Prior to a woman's enrollment in the study, the Informed Consent Form (ICF) will be signed and dated by the participant, or in the case of a minor by the participant's parent(s)/legally acceptable representative, and by the person who conducted the informed consent discussion (i.e., study investigator or their delegate). In the case of a minor, an Assent Form (AF) will also be signed by the study participant. One copy of the signed informed consent for will be retained by the Principal Investigator and one copy will be given to the study participant.

10.2 RESPONSIBILITIES OF MAH

The MAH will be responsible for taking all reasonable steps to ensure the proper conduct of the study and providing adequate resources to this end.

The MAH will also be responsible for submitting the protocol to the National Regulatory Authority (i.e., ANVISA).

10.3 ETHICAL, REGULATORY AND ADMINISTRATIVE RULES

10.3.1 Ethical principles

This study will be conducted in accordance with the latest revision of the Declaration of Helsinki, GPP guidelines, and local regulatory requirements.

Prior to the start of the study, the PI will submit an application to the local EC for review and approval of the study protocol and related documents (e.g., questionnaire, ICF/AF). In addition, any substantial amendment(s) that arise(s) during the study will be submitted for approval to the same EC by the PI.

Copies of all documents submitted to the EC by the PI will be provided to the MAH. The PI will notify the approving IRB/IEC of the study's completion.

The MAH will submit, through the PI, an application to the national ethics committee and regulatory body for review and/or approval of the study protocol and related documents in accordance with local regulations.

The study will not start until all necessary EC and regulatory approvals are obtained in accordance with local regulations. In addition, prior to enrollment, the Investigator(s) or their delegate(s) will review the ICF/AF and accompanying Information Sheet with potential participants and obtain their signed ICF/AF.

The approving ECs and regulatory authority will be notified of the completion of the study by the responsible party.

10.3.2 Laws and regulations

When applicable, each study site will ensure all necessary local regulatory submissions (e.g., EC) are performed in accordance with local regulations, including local data protection regulations.

10.3.3 Data privacy and protection

All data collected related to investigators or others persons involved in the study that may be included in the MAH's databases, will be treated in compliance with all applicable laws and regulations including the Global Data Protection Regulation, Brazil's "Código Civil" and the Law 12.527/2011. Participants' nominal data will not be included in any of the research databases to which the MAH will have access. The MAH will take all appropriate measures to safeguard against and prevent access to these data by any unauthorized party.

On the other hand, the research databases to which the MAH will have access will not contain any of the participants' nominal data. As previously mentioned, the latter will be replaced by the participants' unique, anonymized study identification number.

Data collected will be limited to that which is relevant to the study's objectives and/or study validity.

At the start of the study, each participant and their offspring will be assigned a unique anonymized study identifier (i.e., study identification number) by the Study Investigator(s) and all study data collected (questionnaire or medical record review) or abstracted (MoH and DoH electronic databases) will be archived using only the participant's unique study identification number. The list linking the participants' personal/nominal data to their study code will be kept in a secure and locked location and will only be accessible by the Study Investigators and their delegate(s).

Participants' anonymized data will be entered into an encryption and password protected laptop until it is electronically transferred, via a Virtual Protected Network (VPN), to the MAH's research database and, in the case of reportable AEs, to the MAH's PV database. Any participant record or study dataset that is transferred to the MAH or their delegate (i.e., for the purposes of meeting AE reporting obligations or

for analysis) will contain only the unique anonymized study identification numbers (study codes). Participants' nominal data (e.g., name, address, telephone number, email address) or any information that would make them identifiable will not be transferred to the MAH.

Participants will be informed (via the informed consent process) that their anonymized data will be used by the MAH (i.e., for the purposes of meeting AE regulatory reporting obligations and for analysis) or their delegate (i.e., CRO), and/or examined by clinical quality assurance auditors; all of these activities will be undertaken in accordance with local data protection laws.

The participants will be informed that her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the MAH/Sponsor, by the appropriate EC members, and/or by inspectors from regulatory authorities.

The MAH and Study Investigators will take all appropriate measures to safeguard and prevent access to the research data by any unauthorized third party.

10.3.4 Record retention

Study Investigators will be responsible for the secured retention of all study documentation in their possession until the end of the study. Study Investigators will also comply with specific local regulations/ recommendations with regards to study participants record retention.

The MAH will be responsible for the secured retention of all study documentation in their possession for 15 years after the end of the study.

10.3.5 Discontinuation of the study

The MAH can decide at any time and for any reason to discontinue the study; this decision will be communicated in writing to the PI and participating investigator(s). Similarly, should the PI or investigators decide to withdraw from the study, she/he will inform the MAH in writing.

If appropriate, according to local regulations, the local and national EC and Competent Authorities will also be informed.

10.3.6 MAH audits and inspections by competent authorities

The PI and study investigator(s) agree(s) to allow the MAH auditors and/or Competent Authorities inspectors to have direct access to the participants' study records for the purposes of review and audit; it is understood that these persons are bound by professional secrecy and as such, will not disclose any personal identities or personal medical information. The study investigator will make every effort to assist with the performance of audits and inspections, giving access to all necessary facilities, data, and documents.

The confidentiality of the data verified and the protection of the participants will be respected during these inspections.

Any result and information arising from the inspections by the competent authorities will be communicated by the investigator(s) to the MAH.

The Investigator(s) will take appropriate measures, as required by the MAH, to correct all problems found during the audit(s) and/or inspection(s).

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

For the primary data collected (i.e., structured questionnaire and review of medical records):

- All AEs reported, regardless of seriousness or relationship to CYD-TDV, spanning from the signature of the ICF/AF until the end of the study (as defined by the protocol for each patient) will be collected by the investigators or their delegate(s) and reported to the MAH within an expedited time frame.

For the secondary data collected (i.e., external MoH and DoH databases from Brazil):

- These external databases will be imported independently of the primary data collection process and are characterized as secondary use of data previously collected from healthcare professional for other purposes. As per EMA's Guidelines on Good Pharmacovigilance Practices (GVP), Module VI-Management and Reporting of Adverse Reactions to Medicinal Products, the reporting of AEs in the form of ICSRs is not required for non-interventional study design (GVP VI.C.1.2.1.b).[12]

11.1 SAFETY INSTRUCTIONS

All events will be managed and reported in compliance with all applicable regulations.

11.1.1 Definitions of adverse event and serious adverse event (SAE)

An **Adverse Event** is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.[13]

The worsening of an existing sign or symptom is also considered as an AE. Therefore, an AE may be:

- A new illness;
- The worsening of a concomitant illness;
- An effect of vaccination, including the comparator;
- A combination of the above.

Routine health care visits for pre-existing conditions, routine check-ups, medication prescription renewals, and stable pre-existing conditions as well as planned hospitalizations for elective surgery will not be recorded as AEs. Worsening of the documented pre-existing condition will be a reportable AE.

Surgical procedures are not adverse events; they are the action taken to treat a medical condition. It is the condition leading to the action taken that is the adverse event (if it occurs during the study follow-up period). Medical conditions leading to surgery that started prior to the study but that did not worsen during the study will not be reported as AEs.

A **Serious Adverse Event** is any untoward medical occurrence that at any dose:

- Results in death or;
- Is life-threatening or;
  Note: The term "life-threatening" in the definition of "serious" refers to an event for which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe;
- Requires inpatient hospitalization or prolongation of existing hospitalization or;
- Results in persistent or significant disability/incapacity or;
- Is a congenital anomaly/birth defect;
- Is a medically important event;
- Is a suspected transmission of infectious agent; is any suspected transmission of an infectious agent via a medicinal product (eg, product contamination).

Serious and severe are not synonymous. The term severe is often used to describe the intensity of a specific event. This is not the same as serious which is based on patient / event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness, not severity, serves as a guide for defining regulatory reporting obligations.[13]

Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in situations other than those described above, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed in the definition above.

The pregnancy registry will actively collect AEs specific to the pregnancy, birth, neonatal and infant outcomes of interest, in addition to any maternal AEFI. Pregnancy itself is not considered as an AE, but any complications experience during pregnancy will be considered as AEs, and in some cases could be considered SAEs. The following AEs are always considered SAEs: major congenital malformation, low birth weight, pre-eclampsia, eclampsia, gestational diabetes, preterm delivery, fetal death/stillbirth, death in utero, spontaneous abortion/miscarriage, ectopic pregnancy, elective abortion for medical reason, termination of pregnancy for fetal anomaly (TOPFA), hospitalized dengue, motor-developmental anomalies, and maternal death.

11.1.2 Collection of information on misuse and pregnancy exposure

Misuse: The registry will collect vaccine administration related data including the number of doses received during the pregnancy and overall (secondary objective). As such, the registry will capture misuse with regards to extra doses administered. The study final report will summarize the data on misuse captured by the registry.

Pregnancy exposure: The registry is a study specifically to follow-up pregnant women exposed to CYD-TDV during pregnancy. As such, CYD-TDV pregnancy exposure will not be reported individually but will either be reported by the data management CRO to the MAH/Sponsor's Pharmacovigilance Department on a quarterly basis as line listings or via automated electronic transfers from the eCRF.

11.1.3 Obligations of the Investigator regarding safety reporting

11.1.3.1 Adverse events collection

All AEs regardless of the relationship to CYD-TDV, spanning from the signature of the ICF until the end of the collection period as defined by the protocol for each participant will be recorded in the corresponding section of the eCRF (as described below) **immediately** (within 24hours of identification) if an SAE and within 30 days of detection for a non-serious AE.

11.1.3.2 Adverse event reporting to the MAH/MAH representative

In case of serious adverse events:

- The information related to the SAE will be entered within 24 hours of identification in the appropriate section of the e-CRF; the system will automatically send the notification to the MAH/MAH representative after approval of the report by the Investigator or their delegate(s) within the e-CRF, or automatically after a pre-specified delay.
- When available, send (preferably by fax or e-mail) the photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the MAH whose name, fax number and email address appear on the first page of this Protocol. Care should be taken to ensure that the participant's identity is protected and that the participant's unique study identification number is included in the report. For laboratory results, include the laboratory normal ranges.
- When available, all further data updates will be recorded in the e-CRF as appropriate, and further documentation/additional information (e.g., laboratory data, concomitant medication, patient status) will be sent to Sanofi Pasteur SA, Global PharmacoVigilance Department representative (by fax + 33 4 37 37 71 32 or e-mail PV.outsourcing@sanofi.com) within 24 hours of becoming aware of the SAE. Every effort will be made to further document fatal or life threatening SAEs within the week (7 days) following initial notification.

A back-up plan will be used (using paper flow) in the event that the e-CRF system is not working at the time of the case submission. In such circumstances, the investigator or their delegate will notify the MAH representative using the paper version of AE page of eCRF. The form should be sent either by fax: + 33 4 37 37 71 32 or in a password protected PDF format to PV.outsourcing@sanofi.com. This form can also be sent by express mail to: Sanofi Pasteur SA, Global PharmacoVigilance Department, 14 Espace Henry Vallée, 69007 Lyon, France.

When the electronic reporting system becomes available, the Investigator or their delegate(s) will transcribe the information from the paper version of the eCRF AE pages into the EDC system.

In case of non-serious adverse events:

- The information related to the AE will be entered within 30 days of identification in the appropriate section of the e-CRF; the system will automatically send the notification to MAH/MAH representative after approval of the report by the Investigator or their delegate(s) within the e-CRF or automatically after a pre-specified delay.

11.2 SAFETY OBSERVATIONS

Any SAE occurring any time after vaccination with CYD-TDV and considered by the Investigator(s) to be caused by CYD-TDV with a reasonable possibility, will be reported to regulators by the MAH/MAH representative.

11.3 OBLIGATIONS OF THE MAH

By design, it will not be possible to obtain causality assessments from the reporters, since study investigators collecting the safety data are not the participants' routine healthcare providers and the research personnel will not be able to carry out this assessment based on the information collected during the structured interviews. As such, to comply with country-specific AE reporting requirements, the causality assessment will be undertaken by the MAH via the established MAH process. The causal relationship between the AE and CYD-TDV pregnancy exposure will be evaluated using the following definitions:

- "Not related": The AE is clearly / most probably caused by other etiologies such as an underlying condition, therapeutic intervention, or concomitant therapy; or the delay between vaccination and the onset of the AE is incompatible with a causal relationship; or the AE started before the first vaccination.[13]
- "Related": There is a "reasonable possibility" that the AE was caused by the vaccination, meaning that there is evidence or arguments to suggest a causal relationship.[13]

The MAH will report safety data to health authorities according to Directive 2001/83/EC and in accordance with all applicable local and global regulations. All SAEs will be submitted to the relevant Health Authorities (e.g., ANVISA, European countries) within 15 calendar days of the date of receipt, and all non-serious AEs will be submitted within 90 days of the date of receipt. Other regulatory safety data submissions will be performed in accordance with applicable regulations in the countries where the sponsor is the "MAH".

The information pertaining to AEs contained in the GPV database will be reconciled with that in the study database.

The MAH will report all safety observations made during the conduct of the study in the final study report.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 OWNERSHIP AND USE OF DATA AND STUDY RESULTS

Unless otherwise specified by local laws and regulations, the MAH/Sponsor retains ownership of data, results, reports, findings, and discoveries related to this study.

The data analysis will be performed either by Sanofi Pasteur or by a CRO.

The MAH/Sponsor reserves the right to use the data from the present study for any purpose related to the stated study objectives or to fulfill regulatory reporting obligations, including the one to submit the study data to the Competent Authorities of any country in the form of a study report.

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APPENDICES

APPENDIX 1. LIST OF STUDY INVESTIGATORS

Site	Name and contact information	Role	Expertise
Paraná	[redacted]	[redacted]	Medicine, Epidemiology, Preventative Medicine, Maternal and Child Health
	[redacted]	[redacted]	Medicine, Pediatrics, Epidemiology, Maternal and Child Health
	[redacted]	[redacted]	

APPENDIX 2. PREGNANCY RELATED ADVERSE EVENTS OF SPECIAL INTEREST

Outcome	Description
Pregnancy outcomes	
Ectopic pregnancy	• Pregnancy with fertilized egg implanted and maturing outside the uterus; • Based on clinician assessment as recorded in the medical record or databases
Pregnancy loss	
Spontaneous abortion/miscarriage	• Fetal death with expulsion at <20 weeks of gestation or at weight <500 g if gestational age is unknown; occurred naturally (without outside interference); • Based on clinician assessment as recorded in the medical record or databases
Abortion, unspecified	• Premature expulsion of the embryo or a non-viable fetus where the type of abortion (spontaneous or elective) is not mentioned; • Based on clinician assessment as recorded in the medical record or databases
Abortion, medically indicated	• Abortion brought on intentionally; includes therapeutic abortion when pregnancy is a threat to the mother's life and/or is the result of sexual assault; • Based on clinician assessment as recorded in the medical record or databases
Termination of pregnancy for fetal anomaly (TOPFA)	• Abortion brought on intentionally when the embryo/fetus presents an abnormality
Stillbirth/fetal death	• Delivery of a dead fetus at ≥20 weeks of gestation or in fetus weighing >500 grams if gestational age is unknown; • Based on clinician assessment as recorded in the medical record or databases
Death in utero	• Fetal death without expulsion at < 20 weeks of gestation; • Based on clinician assessment as recorded in the medical record or databases
Complications of pregnancy	
Hypertensive disorders	All with onset at ≥20 weeks gestation
Gestational hypertension	• Hypertension (sustained blood pressure ≥140/90 mmHg) that develops during pregnancy in previously normotensive woman; • Based on clinician assessment as recorded in the medical record or databases
Preeclampsia	• Gestational hypertension with proteinuria (>300mg in 24 hrs); • Based on clinician assessment as recorded in the medical record or databases

Eclampsia	• Preeclampsia with the occurrence of seizures in women without prior history of seizure; or • Based on clinician assessment as recorded in the medical record or databases
Hypertension, not otherwise specified	• Gestational hypertension with no further details; based on clinician assessment as recorded in the medical record or databases
Gestational diabetes	• Fasting plasma glucose > 7.0 mmol/l (>126 mg/dl) or causal plasma glucose >11.1 mmol/l (>200 mg/dl) during pregnancy; • Based on clinician assessment as recorded in the medical record or databases
Placenta previa	• Placental overlying the cervical os; • Based on clinician assessment as recorded in the medical record or databases
Placental abruption	• Premature separation of placenta from uterus; • Based on clinician assessment as recorded in the medical record or databases
Complications of labour, delivery and puerperium	
Premature membrane rupture	• Amniotic sac membrane rupture occurring at <37 weeks gestation around the time of labour; • Based on clinician assessment as recorded in the medical record or databases
Chorioamnionitis	• Acute inflammation of the membranes and chorion of the placenta; diagnosed during delivery hospitalization based on: • Fever >100.4F/38C , plus any two of the following: uterine tenderness, maternal or fetal tachycardia, foul/purulent amniotic fluid; • Based on clinician assessment as recorded in the medical record or databases
Breeched presentation at delivery	• Infant presenting with buttocks or feet first at delivery; • Based on clinician assessment as recorded in the medical record or databases
Postpartum hemorrhage	• Diagnosis based on subjective observation; therefore, clinical definitions vary. Its presence will be based on either: • Clinician assessment as recorded in the medical record(s)/database; or 10% change in hematocrit level between admission and the post-partum period; or need for post-delivery transfusion secondary to blood loss; or signs and symptoms of hypovolemia in the first 24 hours following delivery.
Maternal death	• Maternal death during pregnancy or ≤ 42 days of delivery; derived from maternal date of death and infant DOB

APPENDIX 3. BIRTH OUTCOMES OF SPECIAL INTEREST

Outcome	Definition
Preterm birth	Birth at <37 weeks gestation
APGAR score	
Abnormal	< 7.0 after 5 minutes
Moderately abnormal	4-6 at 5 minutes
Low	0-3 at 5 minutes
Small for gestational age (SGA)	Birth weight <10th percentile
Birth weight	
Low birth weight	1500-2499 g
Very low birth weight	<1500 g

APPENDIX 4. NEONATAL AND INFANT OUTCOMES OF SPECIAL INTEREST

Outcome	Definition
Neonatal outcomes*	
Major congenital abnormality	• Any structural or chromosomal abnormality diagnosed either at birth or in the first 30 days of life; will be assessed on a case-by-case basis, through investigator/delegate review of medical/hospitalization records and agreement by the Advisory Committee
Neonatal intensive care unit admission	• Admission during the birth hospitalization
Neonatal pneumonia	• Diagnosis made during birth hospitalization or subsequent hospitalization if admission occurred within 3 days following discharge from birth hospitalization; based on clinician assessment as recorded in the medical record
Respiratory distress syndrome	• Diagnosis made during birth hospitalization or subsequent hospitalization if admission occurred within 3 days following discharge from birth hospitalization; based on clinician assessment as recorded in the medical record
Transient tachypnea of the newborn	• Diagnosis made during birth hospitalization or subsequent hospitalization if admission occurred within 3 days following discharge from birth hospitalization; based on clinician assessment as recorded in the medical record
Pulmonary hypertension	• Diagnosis made during birth hospitalization or subsequent hospitalization if admission occurred within 3 days following discharge from birth hospitalization; based on clinician assessment as recorded in the medical record
Inpatient encephalopathy	• Encephalopathy diagnosed during birth hospitalization; based on clinician assessment as recorded in the medical record
Neonatal seizures/convulsions	• Diagnosis made during birth hospitalization or subsequent hospitalization if admission occurred within 3 days following discharge from birth hospitalization; based on clinician assessment as recorded in the medical record
Neonatal sepsis	• Diagnosis made during birth hospitalization or subsequent hospitalization if admission occurred within 3 days following discharge from birth hospitalization; based on clinician assessment as recorded in the medical record
Long duration of birth hospitalization	• Duration of birth hospitalization $\geq$4 days
Hospital readmission post-birth hospitalization	• Hospitalization $\leq$30 days of discharge date of birth hospitalization
Neonatal death	• Death occurring in the first 28 days of life

***Infant outcomes*†**	
Congenital abnormality	• Any structural or chromosomal abnormality diagnosed between days 29 and 365 post-birth; will be assessed on a case-by-case basis, through evaluator review and agreement by the Advisory Committee
Hospitalized dengue	• Acute febrile illness with a diagnosis of dengue (suspected or confirmed) requiring hospital admission
Death	• Death occurring between days 29 and 365 post-birth

* Occurring or diagnosed in the first 28 days of life.
† Occurring or diagnosed between days 29 and 365 post-birth.

APPENDIX 5. BASELINE CHARACTERISTICS

Maternal baseline characteristics	Type of variable
Gestational age at CYD-TDV pregnancy exposure	Obtained from SI-PNI AEPV database
Mean (SD), weeks	
Median, weeks (25th & 75th percentile)	
Year of CYD-TDV pregnancy exposure	Derived from date of CYD-TDV pregnancy exposure
2016	
2017	
2018	
2019	
Socio-demographics	
Age at conception, years	Collected from questionnaire & verified using DOB and date of first CYD-TDV vaccination during pregnancy
Mean (SD), years	
Median (25th & 75th percentile), weeks	
1st quartile	
2nd quartile	
3rd quartile	
4th quartile	
BMI (at time of first CYD-TDV vaccination during pregnancy)	Derived from height, weight & age at cohort entry (first vaccination during pregnancy), and sex
<5th percentile (underweight)	
5th to <85% percentile (normal)	
85th to <90 percentile (overweight)	
≥ 90th percentile (obese)	
BMI (at time of first CYD-TDV vaccination during pregnancy)	Derived from height, weight & age at cohort entry (first vaccination during pregnancy), and sex
<18.5 (underweight)	
18.5 to <25 (normal)	
25 to <30 (overweight)	
≥30 (obese)	
Smoking status (at time of first CYD-TDV vaccination during pregnancy)	Collected from the questionnaire
Never smoker	
Past smoker	
Time since stopped	
Mean (SD), months/years	
Median (25th & 75th percentile), months/years	
Current smoker (during CYD-TDV exposed pregnancy)	
In the month before the pregnancy (yes/no)	
During the first trimester (yes/no)	
During the second trimester (yes/no)	
During the third trimester (yes/no)	
Alcohol consumption (during CYD-TDV exposed pregnancy)	Collected from the questionnaire
In the month before the pregnancy (yes/no)	
During the first trimester (yes/no)	
During the second trimester (yes/no)	
During the third trimester (yes/no)	
Highest level of education (at time of first CYD-TDV vaccination during pregnancy)	Collected from the questionnaire
None	
Primary school	

High school	
University/College	
Postgraduate	
Marital status (at time of first CYD-TDV vaccination during pregnancy)	Collected from the questionnaire
Single	
Married/Common law	
Divorced	
Widowed	
Household income (at time of CYD-TDV pregnancy exposure)	Collected from the questionnaire (minimum wage/month; SM equivalent ~ $300 USD)
<1 SM	
1 to <3 SM	
≥3 to <5 SM	
≥5 to <10 SM	
≥ 10 SM	
Unknown/not reported	
Obstetrical and medical history (prior to first CYD-TDV vaccination during pregnancy)	
Gravidity	Collected from the questionnaire; total number of confirmed pregnancies regardless of the outcome
None	
1	
≥2	
Parity	Derived from Gravidity & question on number of pregnancies births Collected from the questionnaire; total number of births with >20 weeks gestation
None	
1	
≥2	
Previous miscarriage/spontaneous abortion (yes/no)	Collected from the questionnaire
Previous preterm birth (yes/no)	Collected from the questionnaire
Previous dengue infection	Collected from the questionnaire
Unknown	
Confirmed (describe method)	
Clinically diagnosed/unconfirmed	
Preexisting comorbidities (yes/no)	Collected from the questionnaire; confirmed using medical record review and/or health databases when available
Hypertension	
Diabetes	
Type I diabetes	
Type II diabetes	
Pulmonary disease (specific type)	
Heart disease (specify type)	
Renal disease (specify type)	
Vaccination and medication history	
Receipt of other vaccine(s) during pregnancy (specify)	Collected from the questionnaire, as well as from the "vaccination card" and/or "prenatal booklet" when available
Receipt of medications during pregnancy (specify)	Collected from the questionnaire; included prescription and non-prescription medications
Characteristics of prenatal care and delivery	
Gestational age at first prenatal visit, weeks	Derived from gestational age at first CYD-TDV vaccination

	during pregnancy & date of first prenatal visit; the latter should be available from either SISPRENATAL or the prenatal booklet
Number of prenatal care visits, mean (SD)	Collected from either SISPRENATAL or the prenatal booklet when available
Referral to specialist care (specify type of specialist)	Collected from the questionnaire and confirmed using SISPRENATAL or the prenatal booklet when available
Number of ultrasounds, mean (SD)	Collected (if data is available)
Index of prenatal care	Derived from number of prenatal care visits recorded in the prenatal booklet and/or SISPRENATAL when available
Adequate/plus (≥7 visits)	
Intermediate (3-6 visits)	
Inadequate (<3 visits)	
Hospitalization(s) during pregnancy	Collected from the questionnaire; confirmed using SISPRENATAL or the prenatal booklet or review of hospitalization records when available
Hospitalization <20 weeks gestation	
None	
1	
≥2	
Hospitalization ≥20 weeks gestation	
None	
1	
≥2	
Emergency Department (ED) visit(s) during pregnancy	Collected from the questionnaire; confirmed using SISPRENATAL or the prenatal booklet or review of hospitalization records when available
ED visit <20 weeks gestation	
None	
1	
≥2	
ED visit ≥20 weeks gestation	
None	
1	
≥2	
Method of delivery	Collected from questionnaire; confirmed using SINASC and/or birth hospitalization record if available
Vaginal	
Cesarean	
Planned	
Emergency	

APPENDIX 6. DATA COLLECTION AND COLLECTION SCHEDULE

	FOLLOW-UP OF MATERIAL & PREGNANCY OUTCOME Enrollment until end of pregnancy					FOLLOW-UP OF OFFSPRING OUTCOMES Up to 12 months past-birth		
	Retrospective Follow-up *	Prospective follow-up				Prospective follow-up		
Data collected		Recruitment visit/contact	1st trimester week 12 (± 2 wks)	2nd trimester week 27 (± 2 wks)	3rd trimester week 40 (± 2 wks)	0-3 months (± 1 month)	Month 6 (± 1 month)	Month 12 (± 1 month)
1. Informed consent	X	X						
2. Assessment of inclusion/exclusion criteria	X	X						
3. Collection of baseline characteristics	X	X						
4. Allocation of unique participant ID number	X	X						
5. Schedule interview with mother	X	X	X	X	X	X	X	X
6. Collection of maternal AEs	X		X	X	X			
7. Collection of pregnancy outcomes	X		X	X	X			
8. Review of prenatal booklet	X		X	X	X			
9. Collection of birth outcomes	X					X	X	X
10. Collection of neonatal & infant outcomes	X					X	X	X

* Data collection will occur only once since data is retrospective; however, it may be necessary to contact the mother/legal guardian post-interview for clarification purposes