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Dengue vaccination during pregnancy – An overview of clinical trials data

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ABSTRACT

Background: The live, attenuated, tetravalent dengue vaccine (CYD-TDV) is licensed in several endemic countries and contraindicated during pregnancy. Inadvertent vaccination during pregnancy may occur during clinical trials that include women of childbearing age. The potential risk associated with dengue vaccination in pregnancy remains unknown. We describe pregnancy outcomes following inadvertent dengue vaccination in pregnancy from CYD-TDV trial data.

Methods: Data were collected from trials conducted as part of the CYD-TDV clinical development. Women who received CYD-TDV or placebo during the pre-specified pregnancy risk window (from 30 days before the date of their last menstrual period to end of pregnancy) were considered as exposed; pregnancies occurring in non-risk periods during the trials were considered to be non-exposed. Pregnancy losses were defined as abortion (spontaneous or unspecified), death in utero, and stillbirth.

Results: 615 pregnancies were reported from 19 CYD-TDV trials: 404 in the CYD-TDV arm, and 211 in the placebo arm. Exposure could not be determined for 7 pregnancies (5, CYD-TDV; 2, placebo). In the CYD-TDV arm, 58 pregnancies were considered as exposed. Most of these (n = 47, 81%) had healthy live births; 6 (10.3%) had pregnancy losses; 3 underwent elective termination and 2 had unknown outcome. In the placebo group, 30 pregnancies were considered exposed. Most of these (n = 25, 83%) had healthy births; 4 (13.3%) had pregnancy losses; and 1 had elective termination. Among non-exposed pregnancies, most resulted in healthy live births; 23/341 (6.7%) in the CYD-TDV group and 17/179 (9.5%) in the placebo group had pregnancy losses. Most reported pregnancy losses were in women considered high-risk for adverse pregnancy outcome, primarily due to young age.

Conclusion: In the small dataset assessed, no evidence of increased adverse pregnancy outcomes has been identified from inadvertent immunization of women in early pregnancy with CYD-TDV compared with the control group.

1. Introduction

Dengue is a mosquito-borne viral infection that, while asymptomatic in the majority of cases, can lead to clinical illness ranging from a non-specific viral syndrome to severe, fatal haemorrhagic disease [1]. Worldwide, an estimated 390 million cases of dengue virus infection occur every year, of which around 100 million are associated with clinical manifestation [2,3]. The majority of cases occur in dengue-endemic regions, particularly Asia, India, Central and South America, and Africa [2].

There is no specific treatment for dengue and vector control measures alone have generally proved insufficient in view of the continued worldwide spread of dengue [3]. A live, attenuated, tetravalent vaccine against dengue (CYD-TDV) was first approved in Mexico in December 2015, for individuals from 9 years of age and is now used in a number of endemic countries [4,5]. Recent additional data have indicated that in seronegative participants at baseline, an elevated risk of hospitalized virologically-confirmed dengue was observed during the third year after first vaccination in 9–16-year-olds [6].

The risk of women contracting dengue during pregnancy is a growing concern as the number of epidemics and geographical range of disease transmission increase [2]. Previous studies have suggested that dengue infection during pregnancy is associated with increased risks of both a more severe course of disease and

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adverse pregnancy outcomes [7,8]. Thus, women at or before childbearing age, from endemic areas, are an important target group for vaccination with any dengue vaccine.

As with most live attenuated vaccines, due to a theoretical risk to the foetus, CYD-TDV is contraindicated in pregnancy. Preclinical data have not revealed any teratogenic effects in the offspring of animals vaccinated with CYD-TDV during pregnancy [9]. In humans, no studies or analyses have been performed to specifically evaluate the safety of dengue vaccination during pregnancy. Pregnancy is a strict exclusion criterion in all CYD-TDV clinical trials and a negative pregnancy urine test is required before each vaccination. Despite these precautions, a limited number of women in CYD-TDV clinical trials have been inadvertently vaccinated during pregnancy, mostly before, or in the few days following, conception. The close monitoring of these pregnancies and pregnancy outcomes may provide some insight into the potential risks of vaccinating during pregnancy.

Here, we describe data from pregnancy outcomes documented to date from the inadvertent vaccination of women in early pregnancy during the clinical development of CYD-TDV.

2. Methods

2.1. Studies

The current analysis was based on 19 Sanofi Pasteur-sponsored clinical studies with CYD-TDV: CYD04; CYD05; CYD06; CYD10; CYD11; CYD12; CYD13; CYD14; CYD15; CYD17; CYD22; CYD23; CYD57; CYD24; CYD28; CYD30; CYD32; CYD47; and CYD51. The cut-off for the collection of pregnancy data was 01 September 2015. All included studies were completed at the time of analysis, with the exception of efficacy studies CYD14, CYD15, and CYD23, for which only data from the active phase (unblinded data from the first 25 months of the study) were included in the analysis.

Eligible studies and key characteristics, including primary citations, where available, are listed in Table S1. Specific study design and enrollment characteristics with inclusion/exclusion criteria are described in detail in the original publications [4,5,10–24]. In most of the included trials, dengue vaccine was planned to be administered subcutaneously in a 3-dose schedule. Pregnant women were ineligible for inclusion. All female participants were required to be of non-childbearing potential (post-menopausal for at least 1 year, surgically sterile, using an effective method of contraception, or being abstinent from at least 4 weeks prior to the first vaccination and until at least 4 weeks after the last vaccination). In addition, a negative pregnancy test was required before each vaccination. Women who became pregnant during the study did not receive further vaccinations, but were followed up for safety assessments until delivery and for the entire period of the study as planned.

Studies were conducted in accordance with the Declaration of Helsinki and the International Conference on the Harmonization of Good Clinical Practice. The study protocols were approved by the respective Institutional Review Boards or Independent Ethics Committees at each study site. Written informed consent was obtained from all participants or their parents/guardians. Data on pregnancy outcomes from CYD-TDV clinical trials were regularly reviewed by the Independent Data Monitoring Committee (IDMC).

2.2. Pregnancy cases and pregnancy outcomes

Pregnancy cases were categorised for the current analysis according to exposure or non-exposure to CYD-TDV (Fig. 1). Given that some pregnancies were reported with unknown date of last menstrual period (LMP), the analysis was done using estimated conception date (ECD), which was calculated as LMP + 14 days if LMP was reported; if no LMP was reported, the conception date was defined based on reported gestational age at ultrasound examination. Exposed pregnancy cases were defined as those with CYD-TDV administered during pregnancy, including the risk window from 30 days before the LMP date or 44 days before the ECD. They were then further categorised according to those exposed during the conservative risk window starting 7 days after LMP or 7 days before the estimated date of conception ('exposed and pregnant') and those who received CYD-TDV during the period from 30 days before to 7 days after LMP or from 44 days to 7 days before estimated conception date ('exposed and not pregnant'). All other pregnancies, i.e. those with vaccination falling outside of the risk window, were considered to be 'non-exposed'; these pregnancies may have occurred during non-risk periods throughout the study, between scheduled doses or up to 1 year following the third dose. Placebo recipients were categorised according to exposure or non-exposure to placebo during pregnancy based on the same principles. These definitions of exposure were endorsed by the IDMC.

For all included studies, efforts were made to follow all pregnancies until delivery. The number of pregnancy cases that were reported during these trials and their outcomes were recorded.

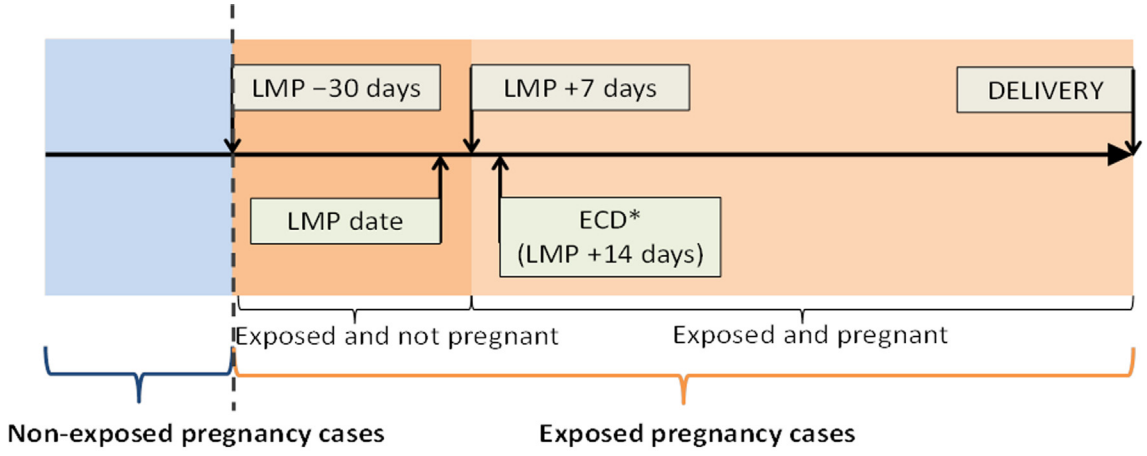

Fig. 1. Classification of exposed versus non-exposed pregnancy cases.