These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor: Sanofi Pasteur **Drug substance(s):** Fluzone Trivalent Intradermal Influenza Vaccine (TIV-ID) and Fluzone Quadrivalent Intradermal Influenza Vaccine (QIV-ID)	**Study Identifiers:** U1111-1161-3485, NCT02554409 **Study code:** QID02
Title of the study: Fluzone® Intradermal Vaccine Pregnancy Registry	
Study Centers: United States (US).	
Study period: Date of study start date: 1/Sep/2011 Date of study end date: 30/Apr/2019 Study Status: Completed	
Objectives: The current summary represents an accumulation of all pregnancy exposure information obtained through the Fluzone ID pregnancy registry and can be used to supplement pre-existing safety data obtained through past clinical trials to supplement the limited data obtained from pregnancy exposure during the clinical development program. The Fluzone ID Registry (QID02) initially created to monitor exposures to TIV-ID commenced in September 2011 and was maintained after QIV-ID was introduced in 2015. As the registry is descriptive in nature, no pre-specified hypotheses were formulated or tested since the principal objective was to monitor pregnancy exposures and to investigate any safety signals that arose in relation to either the mother or infant. All data were routinely monitored through an annual Periodic Benefit Risk Evaluation Report (PBRER) used to summarize all safety information related to the family of Fluzone products. The current summary fulfills the post-marketing commitment made to the US FDA for both ID vaccines.	
Methodology: The Fluzone ID Pregnancy Registry was based on passive PV surveillance as it captured only voluntary reports from health care providers and consumers following immunization during pregnancy. The vaccine prescribing information that accompanies all products contains a recommendation to report all cases of exposure during pregnancy regardless of the occurrence of an adverse event (AE). Reports were filed by calling Sanofi Pasteur's registry affiliated toll-free number (1-800-822-2463), which was listed on the vaccine package insert or could be found on the registry information website (https://www.sanofipasteurpregnancyregistry .com/). After the receipt of the initial exposure report, a structured Pregnancy Report Form was sent to the original reporter to gain additional information on the expecting mother's pregnancy and medical history. If the form was not returned by the reporter, three follow-up attempts were made by Sanofi Pasteur. If the pregnancy then resulted in a live birth, a similarly structured Infant Data Collection Form was sent to the reporter six months after the estimated date of delivery to assess the health of the infant and the occurrence of congenital anomalies or other presenting medical conditions. If the initial reporter did not have information on the infant, an attempt was made to obtain the contact information of the infant's pediatrician or doctor. If contact information was available, three follow-up attempts were also made with the child's physician or the hospital where the delivery occurred in the case of unreturned forms. The initial pregnancy exposure reports were classified and separated for analysis depending on whether the case was prospective or retrospective. For a case to be considered prospective, the initial report must have been made following vaccine exposure but prior to any knowledge of the pregnancy outcome, ascertained through various prenatal tests (eg. targeted ultrasound, amniocentesis, etc). If prenatal testing had already occurred prior to the filing of the exposure report, it was	

assumed that the pregnancy outcome was known and therefore the case was considered retrospective in nature. Reports were considered prospective if there was no available information on the time of prenatal testing. All AEs reported were classified and coded in accordance with the preferred terms found in the Medical Dictionary of Regulatory Activities (MedDRA). Following the stratification of prospective and retrospective reports, descriptive statistics were conducted to analyze the frequencies of various outcomes among those exposed during pregnancy.

Number of participants: Enrolled: 87

Evaluated: 87

Participant selection:

The population of interest included all women exposed to either TIV-ID or QIV-ID during their pregnancy or within 30 days prior to their last menstrual period (LMP) for which a report was filed. During the clinical trials conducted with the Fluzone ID vaccines some women were inadvertently exposed but as these reports are not spontaneous in nature, they were not included in the primary analysis.

Study products:

Fluzone Trivalent Intradermal Influenza Vaccine (TIV-ID)

Fluzone Quadrivalent Intradermal Influenza Vaccine (QIV-ID)

Duration of study: September 2011 - April 2019.

Criteria for evaluation:

For the purposes of this study, outcomes comprised any AE that occurred following the vaccination of a pregnant woman including both diagnoses and symptoms. All events were then grouped into four categories defined as maternal events, obstetrical outcomes, pregnancy outcomes and neonatal outcomes. Maternal events were defined as any AE impacting maternal health that is independent of the pregnancy itself (eg. vaccination site pain); obstetrical outcomes included those AEs that were directly related to the pregnancy (eg. low birth weight); pregnancy outcomes consisted of AEs related to labour and delivery (eg. still births); and neonatal outcomes directly pertained to the infant and were evaluated at birth or within the first 28 days of life (eg. Apgar score). Outcomes were also assessed for the clinical trial exposure cases in a separate analysis and were based only on the limited number of exposed women.

Statistical methods:

Baseline characteristics were reported using descriptive statistics. Outcomes were assessed using R statistical software version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). Loss to follow-up was accounted for by adjusting the denominators used in the calculation of outcome proportions. Maternal events were based on all exposed cases obtained through the registry; pregnancy and obstetrical related outcomes were based on all women who had recorded follow-up information beyond the initial case report; and neonatal outcomes were based on all cases with follow-up information on the infant.

For each outcome, 95% confidence intervals were calculated so that the precision surrounding each estimate could be considered when interpreting the results. The Agresti-Coull method for binomial proportions was used when applicable, but in some cases the Jefferies method was used for very small proportions.

Summary:

From September 2011 to 30 April 2019, there were 87 reports of exposure to TIV-ID or QIV-ID in pregnant women residing in the US. Baseline characteristics were calculated for prospective cases as the single retrospective case was examined separately (Table 1). The average age of the pregnant women captured in the registry was 31.49 years old with over 93% receiving TIV-ID. The majority of cases (81.39%) were reported in 2012 and 2013, with most reported by either pharmacists or “other” HCPs.

1.1.1 Table 1: Fluzone ID Case Report Characteristics

Variable Name	Count	Percent (N=86)
Age of Pregnant Women		
Average (Years)	31.49	/
Range (Years)	18 - 46	/
Vaccine Administered		
Fluzone Trivalent Intradermal Influenza Vaccine	80	93.02
Fluzone Quadrivalent Intradermal Influenza Vaccine	6	6.98
Case Seriousness		
Serious	5	5.81
Non-Serious	81	94.19
Primary Reporter Type		
Pharmacist	34	39.53
Physician	2	2.33
Consumer/Non-HealthCare Professional	8	9.30
Other Health Professional	42	48.84
Trimester at Exposure		
First Trimester	20	23.26
Second Trimester	20	23.26
Third Trimester	13	15.12
Unknown	33	38.37
Event Outcome		
No Adverse Event	15	17.44
Not Recovered/Not Resolved	6	6.98
Recovered/Resolved	4	4.65
Unknown	61	70.93
Case Report Year		
2011	1	1.16
2012	30	34.88
2013	40	46.51
2014	8	9.30
2015	5	5.81
2016	2	2.33

All 86 prospective exposure cases were included in the analysis of maternal AEs. No AE was reported in 61 pregnant women, while a total of 32 maternal AEs were reported across 19 pregnant women (Table 2). It should be noted that some women experienced more than one AE, but each AE was treated independently and therefore the 32 maternal events represent the total number of reactions (not individual cases). Vaccination site inflammation was the most commonly reported maternal AE (8.14%; 95% confidence interval [CI] 3.75%, 16.11%), followed by vaccination site pain (3.49%; 95% CI 0.77%, 10.18%). Vaccination site erythema, other vaccination site reactions and other events were all reported with equal frequencies (2.33%; 95% CI 0.14%, 8.59%). The remainder of the maternal AEs including conditions such as insomnia and syncope occurred only once (1.16%; 95% CI 0.13%, 5.31%).

1.1.2 Table 2: Maternal Adverse Events Following Fluzone ID Vaccination

	N*	%	95% CI
Vaccination Site Inflammation	7	8.14	3.75, 16.11
Vaccination Site Pain	3	3.49	0.77, 10.18
Vaccination Site Erythema	2	2.33	0.14, 8.59
Vaccination Site – Other Reaction	2	2.33	0.14, 8.59
Other Events	2	2.33	0.14, 8.59
Pyrexia	1	1.16	0.13, 5.31**
Insomnia	1	1.16	0.13, 5.31**
Vaccination Site Edema	1	1.16	0.13, 5.31**
Vaccination Site Pruritus	1	1.16	0.13, 5.31**
Vaccination Site Warmth	1	1.16	0.13, 5.31**
Vaccination Site Induration	1	1.16	0.13, 5.31**
Syncope	1	1.16	0.13, 5.31**
Seizure	1	1.16	0.13, 5.31**
Chills	1	1.16	0.13, 5.31**
Myalgia	1	1.16	0.13, 5.31**
Erythema	1	1.16	0.13, 5.31**
Rash	1	1.16	0.13, 5.31**
Pruritus – Generalized	1	1.16	0.13, 5.31**
Induration	1	1.16	0.13, 5.31**
Pain – In Extremity	1	1.16	0.13, 5.31**
Pain – Generalized	1	1.16	0.13, 5.31**

*Among all prospectively exposed pregnancies (N=86); some women experienced 1+ adverse events

**Jefferies method used to ensure intervals between 0, 1 were attained as per the binomial distribution

Due to the low frequency of pregnancy and obstetrical outcomes, both were combined for analysis. It was deemed appropriate to use only the pregnancies with follow-up information beyond the initial report as the denominator for both, which was 26 pregnancy exposure cases. A total of six individual AEs were reported by four different pregnant women within this group including intrapartum hemorrhage, premature labour, pre-eclampsia, diagnosis of a shortened cervix, gestational diabetes and spontaneous abortion (3.85%; 95% CI 0.42%, 16.60%). The full table of pregnancy and obstetrical outcomes can be seen in Table 3.

1.1.3 Table 3: Pregnancy and Obstetrical Outcomes Following Fluzone ID Vaccination

	N*	%	95% CI
Intrapartum Hemorrhage	1	3.85	0.42, 16.60**
Premature Labour	1	3.85	0.42, 16.60**
Pre-eclampsia	1	3.85	0.42, 16.60**
Shortened Cervix	1	3.85	0.42, 16.60**
Gestational Diabetes	1	3.85	0.42, 16.60**
Spontaneous Abortion	1	3.85	0.42, 16.60**

*Among all pregnancies with follow-up information after initial report creation (N=26)

**Jefferies method used to ensure intervals between 0, 1 were attained as per the binomial distribution

Follow-up information pertaining to birth outcomes was obtained for 10 of the exposure cases with two pregnancies resulting in the birth of twins. This yielded information on a total of 12 births, all resulted in the delivery of normal infants (100.00%; 95% CI 81.47, 100.00).

1.1.4 Table 4: Birth Outcomes Following Fluzone ID Vaccination

	N*	%	95% CI
Normal Baby	12	100.00	81.47, 100.00**

*Among all pregnancies with known birth outcomes (N=12)
***Jefferies method used to ensure intervals between 0, 1 were attained as per the binomial distribution

Neonatal outcomes included all pregnancy exposure cases that resulted in a live birth, for a total of 12 infants. Eight of the infants were classified as having a normal birth weight (66.67%; 95% CI 38.80%, 86.45%), while three had a low weight at birth (25.00%; 95% CI 8.27%, 53.85%). Of the available data on Apgar scores five minutes following delivery, five were within the normal range defined as a score above seven (41.67%; 95% CI 19.26%, 68.11%), while only one with a low score was reported. Neonatal outcomes can be seen in Table 5.

1.1.5 Table 5: Neonatal Outcomes Following Fluzone ID Pregnancy Exposed Vaccination

	N*	%	95% CI
Birth Weight			
Normal (2500-4000g)	8	72.73	42.89, 90.80
Low (1500-2499g)	3	27.27	9.20, 57.11
Very Low (<1500g)	0	/	/
Apgar Score (After 5 Minutes)	**N****		
Normal (> 7)	5	83.33	41.78, 98.86
Low (5-7)	1	16.67	1.86, 55.81***

*Among all infants with reported birth weights (N=11)
**Among all infants with reported Apgar Score (N=6)
***Jefferies method used to ensure intervals between 0, 1 were attained as per the binomial distribution

At the time of receipt of all AEs, medical seriousness was assessed resulting in five cases being classified as serious events .

1.1.6 Table 6: Medically Serious Events Following Fluzone ID Vaccination

	N	Status (As Per Last Follow-Up)
Intrapartum Hemorrhage	1	Recovered
Syncope	1	Unknown
Seizures	1	Unknown
Spontaneous abortion	1	N/A
Gestational Diabetes	1	Recovered

The single retrospective case involved the administration of QIV-ID to a pregnant female during an unknown period of gestation. During vaccine administration by a physician a small amount of solution drained down the arm, no resulting bubble or bump appeared. No AEs were reported and no further follow-up information on pregnancy or neonatal outcomes were obtained.

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