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SHORT REPORT

Seasonal influenza vaccine exposure in pregnancy: 5-year results from a pregnancy registry

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ABSTRACT

The World Health Organization recommends that all pregnant women receive seasonal influenza vaccine. Under a post-authorization safety study protocol (NCT02148211), a pregnancy exposure registry was established in the United States to monitor spontaneously reported pregnancy outcomes in women vaccinated with GSK's seasonal inactivated influenza vaccines (IIVs). From 1 June 2014 to 31 May 2019, 507 pregnancies were prospectively reported: 352 (69.4%) were lost to follow-up and 40 (7.9%) were ongoing. Reported outcomes for the remaining 115 were: 101 (87.8%) live births without congenital anomalies; 3 (2.6%) live births with congenital anomalies; 2 (1.7%) spontaneous abortions with no congenital anomalies; 1 (0.9%) spontaneous abortion with a congenital anomaly; 1 stillbirth with no apparent congenital anomaly; 7 (6.1%) 'Unknown'. Results from 493 prospective reports received via worldwide spontaneous, passive surveillance showed similar outcomes. All cases with congenital anomaly were assessed as not likely/unlikely/unrelated to vaccination. Despite the limited number of cases and outcomes, no safety signal was identified. The study findings are aligned with previously published data and should be confirmed with other robust data sources.

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Influenza infection that occurs during pregnancy can compromise maternal and fetal outcomes.[1] In 2012, the World Health Organization recommended that all pregnant women should receive vaccination against influenza.[2] Inactivated influenza vaccines (IIVs) have subsequently been administered to millions of women during pregnancy, and a wealth of evidence from large observational studies and meta-analyses suggests that IIV vaccination during pregnancy is not associated with an increased risk of adverse outcomes for mothers or fetuses.[3–9]

Patient registries can provide prospective, real-world data arising from routine clinical practice. Compared to routine event surveillance, registries can potentially evaluate large numbers of patients and allow more structured data collection.[10] Pregnancy registries have provided valuable information in the evaluation of the risk of adverse outcomes in women exposed to vaccines during pregnancy, such as vaccines for human papillomavirus,[11,12] anthrax,[13] and varicella.[14] Between 2011 and 2013, GSK initiated 4 pregnancy registries in the United States (US) to monitor adverse maternal and fetal outcomes after exposure to its licensed seasonal IIVs: *Fluarix* and *Fluarix Quadrivalent* vaccines manufactured in Dresden, Germany; and *FluLaval* and *FluLaval Quadrivalent* vaccines manufactured in Quebec City, Canada. All 4 IIVs are classified as Pregnancy Category B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. GSK's licensed seasonal IIVs are split virion IIVS consisting of equal amounts of 3 or 4 monovalent viral antigen bulks prepared from influenza strains A/H1N1, A/H3N2 and 1 or 2 B strains (1 B/Yamagata lineage and/or 1 B/Victoria lineage).[15] In 2014, the existing registries were transitioned to a combined post-authorization safety study (PASS, NCT02148211). The design of the PASS was the same as the existing registries, but brought them together for administrative reasons and in an attempt to improve enrollment. Here we report the 5-year results of the PASS which commenced on 1 June 2014 to the data lock point of 31 May 2019.

This was an exploratory, prospective, observational cohort study (the IIV pregnancy registry). Patients or healthcare professionals were encouraged to voluntarily and prospectively enroll any pregnant woman who had been exposed to 1 of GSK's seasonal IIVs. Pregnant women who voluntarily enrolled in the registry had to sign an informed consent form that allowed GSK to contact their healthcare professional around the estimated delivery date (EDD) for follow-up information.

The registry objectives were to describe the proportion and characteristics of prospectively reported pregnancies with abnormal outcomes in women exposed to IIVs during pregnancy or within 28 days preceding gestation. The registry was advertised through the US Prescribing Information and the GSK registry website, which gave a brief summary of the purpose and intent of the registry

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Clinical Trial Registration: NCT02148211 (www.clinicaltrials.gov).
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along with telephone and fax contact information. Additionally, GSK requested that the same information be posted directly on the website of the US Food and Drug Administration.

A woman was included in the registry if she had been exposed to 1 of GSK's IIVs during pregnancy or within 28 days preceding conception; was a US resident; had an identifiable healthcare professional (including their contact details); and could be identified by GSK or the healthcare professional. Data from registered women were only included in the analysis cohort if the pregnancy was ongoing and the outcome was unknown at the time of the initial report (prospective reporting). Conversely, a retrospective report, defined as when the outcome of the pregnancy (including prenatal test results) was known and abnormal at the time of the initial report, was not included in the analysis cohort.

Initial and follow-up data were collected from pregnant women and/or their healthcare professional using questionnaires. These included an initial notification form, a pregnancy outcome form to be completed within 2 months of the EDD to ascertain outcome of the pregnancy, and a 6 to 12-months post-delivery follow-up form to ascertain the presence of birth defects not previously diagnosed. Follow-up questionnaires could only be completed by healthcare providers and/or their staff. Information about maternal medical and obstetric history, other drug/vaccine exposures, adverse events experienced by the fetus/infant or mother, and infant/neonatal status at birth until 6 and 12 months of age was recorded. Reasonable efforts were made to minimize loss to follow-up, with up to 2 attempts made to obtain additional information from women, healthcare providers and the pediatrician and/or other specialists who had provided healthcare/consultation to the child up until 12 months of age.

Pregnancy outcomes of interest were spontaneous abortion (pregnancy loss before 22 weeks gestation), fetal deaths/stillbirths (loss at or after 22 weeks gestation), elective/therapeutic abortions, and live births. The study outcomes were assessed for the likelihood of a safety signal warranting further investigation against known background rates from external existing systems such as the National Birth Defects Prevention Network, the National Center for Health Statistics and the Metropolitan Atlanta Congenital Defects Program. Potential causal associations between congenital anomalies and vaccination were assessed when data allowed by considering the timing of vaccination in relation to embryogenesis, biological plausibility, and the presence of other potential causal factors.

From 1 June 2014 to 31 May 2019, 507 pregnancies exposed to GSK's IIVs in the US were prospectively reported. There were 84 exposures (16.6%) that occurred during the first trimester, 113 (22.3%) in the second, 91 (17.9%) in the third trimester, and 219 (43.2%) for which the date of exposure was unknown (Table 1). There were 13 pregnancies (2.6%) exposed to *FluLaval*, 59 (11.6%) to *FluLaval Quadrivalent*, 112 (22.0%) to *Fluarix*, and 325 (63.8%) to *Fluarix Quadrivalent* (Table 2).

A total of 352 (69.4%) pregnancies were lost to follow-up, 40 (7.9%) women were still pregnant at the time of last contact (no further information available as on 01 April 2020), and a pregnancy outcome was available for 115 (22.7%) women. Of the remaining 115 pregnancies, 101 (87.8%) resulted in a live birth without congenital anomaly; 3 (2.6%) were live births with congenital anomalies; 2 (1.7%) were spontaneous abortions with no apparent congenital anomalies; 1 (0.9%) was a spontaneous abortion with a congenital anomaly; and 1 (0.9%) was a stillbirth with no apparent congenital anomaly. The pregnancy outcome of 7 (6.1%) women in the registry was reported as 'Unknown' (usually lost to follow-up) (Table 1). Although the sample size was small for some IIVs, the distribution of registered pregnancies by trimester of exposure and outcome was similar for the 4

Table 1. Trimester of exposure and outcomes for IIV-exposed pregnancies in the United States, 2014–2019.

Trimester	First	Second	Third	Unknown	Total
Pregnancy ongoing	7	6	5	22	40
Lost to follow-up	54	67	54	177	352
Live infants without congenital anomalies	19	37	30	15	101
Live infants with congenital anomalies	0	3	0	0	3
SA with no apparent congenital anomalies	1	0	0	1	2
SA with congenital anomalies	1	0	0	0	1
Stillbirth with no apparent congenital anomalies	1	0	0	0	1
Outcome reported as unknown	1	0	2	4	7
Total	**84**	**113**	**91**	**219**	**507**

IIV, inactivated influenza vaccine; SA, spontaneous abortion.

Table 2. Trimester of exposure and outcomes for pregnancies exposed to GSK's seasonal inactivated influenza vaccines.

Trimester	First	Second	Third	Unknown	Total
FluLaval					
Pregnancy ongoing	2	3	0	1	6
Lost to follow-up	1	3	1	0	5
Outcome reported as unknown	0	0	2	0	2
Total	3	6	3	1	13
FluLaval Quadrivalent					
Pregnancy ongoing	0	1	1	6	8
Lost to follow-up	5	5	3	13	26
Live infants without congenital anomalies	4	6	10*	3	23
SA with no apparent congenital anomalies	0	0	0	1	1
SA with congenital anomalies	1	0	0	0	1
Total	10	12	14	23	59
Fluarix					
Lost to follow-up	2	3	3**	103	111
Outcome reported as unknown	0	0	0	1	1
Total	2	3	3	104	112
Fluarix Quadrivalent					
Pregnancy ongoing	5	2	4	15	26
Lost to follow-up	46	56	48**	61	211
Live infants without congenital anomalies	15	31	21*	12	79
Live infants with congenital anomalies	0	3	0	0	3
SA with no apparent congenital anomalies	1	0	0	0	1
SA with congenital anomalies	0	0	0	0	0
Stillbirth with no apparent congenital anomalies	1	0	0	0	1
Outcome reported as unknown	1	0	0	3	4
Total	69	92	73	91	325

SA, spontaneous abortion. * One woman was exposed to both *FluLaval Quadrivalent* and *Fluarix Quadrivalent* during pregnancy, therefore, the same case was included in the respective table of each product. ** One woman was exposed to both *Fluarix* and *Fluarix Quadrivalent* during pregnancy, therefore, the same case was included in the respective table of each product.

IIVs combined, and no patterns or trends were observed (Table 2).

Among adverse pregnancy outcomes there were 4 infants/fetuses with congenital anomalies. One infant had polycystic kidney disease. The mother of this infant had received IIV at 16 weeks gestation, which is after the period of renal embryogenesis that occurs early in the first trimester,[16] and thus a causal association with IIV was deemed unlikely. One infant had a cleft lip and palate at birth. The mother of this infant had received IIV at 16 weeks + 5 days of gestation. The critical period for palatal development is between the 6th and 9th weeks of gestation,[17] and a causal association with IIV is unlikely. One woman who received IIV at 23 weeks gestation delivered twins by cesarean section at 31 weeks. A causal association between vaccination and premature delivery seems unlikely and 'cardiac insufficiency' found in the case is not suggestive of congenital anomaly because the date of vaccination was after the period of cardiogenesis and was likely due to twin-twin transfusion syndrome. One woman who received IIV at 5 weeks gestation experienced spontaneous abortion at 22 weeks. A congenital anomaly was reported to the registry, but no record of a congenital anomaly was noted in any of the source documents submitted, and the dates are not interpretable.

One woman experienced a stillbirth 188 days after receiving IIV. The cause of death was suspected to be presence of nuchal cord (umbilical cord around neck of baby). Based on the nature of the event and time to onset, a causal association with vaccination was ruled out. There was 1 spontaneous abortion in a woman with a history of extensive recreational drug and alcohol exposure and chickenpox prior to the last menstrual period, which confounded the causality assessment. Finally, a 40-year-old woman spontaneously aborted twins the day after receiving IIV (around week 12 of gestation). There was insufficient information for further assessment.

A total of 692 adverse events were reported for all 507 registered pregnancies, of which the vast majority were 'exposure during pregnancy' (504 events) and 'live birth' (103 events) (Supplementary Table 1). Other adverse events classified by Medical Dictionary for Regulatory Activities System Organ Class were: *Injury, poisoning and procedural complications* (29 events), *Pregnancy, puerperium and perinatal conditions* (24 events), *General disorders and administration site conditions* (10 events), *Musculoskeletal and connective tissue disorders* (6 events), *Gastrointestinal disorders* (5 events), *Immune system disorders* (2 cases), *Infections and infestations* (2 cases), *Nervous system disorders* (2 cases), *Psychiatric disorders* (1 event), *Skin and subcutaneous tissue disorders* (1 event), and *Surgical and medical procedures* (1 event). Two adverse events, both *Congenital, familial and genetic disorders*, were reported in infants.

In addition to the US pregnancy registry described above, GSK also receives retrospective notification of seasonal influenza vaccine-exposed pregnancies and their outcomes from global sources through its passive spontaneous adverse event reporting system. To complement the registry results and evaluate the outcomes of all pregnancies exposed to GSKs VIIs worldwide, additional reports of exposed pregnancies were extracted from the worldwide safety database until the cutoff date of 31 May 2019. Among an additional 676 spontaneous reports of influenza vaccine exposure during pregnancy received by GSK from global sources, 493 were prospective (Table 3). Of these, 307 (62.3%) were reported as lost to follow-up. Of the 186 pregnancies with a known outcome; 66 (35.5%) pregnancies were ongoing, 114 (61.3%) resulted in live births with no birth defects, 5 (2.7%) in spontaneous abortion with no birth defects, and there was 1 (0.5%) elective termination without birth defects. There were no reports of birth defects reported among cases reported prospectively to GSK's safety database.

Table 3. Pregnancy outcomes from worldwide spontaneous case reporting.

Pregnancy outcome	Prospective	Retrospective	Not coded	Total
Pregnancy ongoing	66	0	0	66
Lost to follow-up/unknown outcome	307	107	9	423
Live birth without birth defects	114	22	10	146
Live birth with birth defects	0	6*	0	6*
SA without birth defects	5	18	3	26
SA with birth defects	0	0	0	0
Stillbirth without birth defects	0	4	0	4
Stillbirth with birth defects	0	2	0	2
Elective termination without birth defects	1	1	0	2
Elective termination with birth defects	0	1	0	1
Total	**493**	**161**	**22**	**676**

SA, spontaneous abortion. * one case was duplicated.

Among 54 spontaneous retrospective pregnancy reports with a known outcome, 31 reported still birth, spontaneous abortion or birth defects (Table 3). The high proportion of adverse outcomes is not unexpected given that retrospective notification of outcomes following exposure to drugs or vaccines is biased toward reporting the severe and unusual cases.[18,19] There were 8 retrospective cases with birth defects including variant polydactyly (causal association not likely), talipes equinovarus (2 cases: causal association not likely for 1 case and unlikely but indeterminate for the second case), congenital cardiac anomalies and aneuploidy with infectious and immune etiologies and chromosomal anomalies (causal association unlikely), Trisomy 21 and chronic chorioamnionitis (causal association ruled out), Trisomy 21 with group B streptococcal colonization (causal association ruled out), gastroschisis with atrial septal defect (causal assessment not possible as timing of vaccination not known), and congenital syphilis (causal association ruled out).

The risk in the general population of all birth defects meeting Centers for Disease Control and Prevention criteria is approximately 3% of live births.[20] The Collaborative Prenatal Project, using a broader case definition and prospective ascertainment, reports a frequency of 5% to 7%.[21] Most major structural defects originate during the first trimester of pregnancy, which is the critical time for organogenesis.[22] For such defects, exposures occurring in the second or third trimester are not likely to be causally associated.

No safety signal was identified among IIV-exposed pregnant women who reported their pregnancy outcomes to the US registry or through GSKs worldwide safety database.

Pregnancy registries can provide real-time insights into the effect of exposures during pregnancy and can collect accurate

data around the timing of exposure and a variety of prenatal, perinatal and postnatal outcomes for the mother and infant. However, pregnancy registries face particular challenges because they rely on voluntary reporting and are prone to low rates of recruitment and retention. This is particularly the case because the subjects of interest are usually healthy women who expect a positive pregnancy outcome and have little incentive to participate. The logistics of following up on the health of a pregnant woman and their infant by relying solely on the voluntary submission of information by their obstetrician or pediatrician are complicated, and response rates can be low, contributing to poor retention rates.[23] Rates of loss to follow-up vary widely and tend to be higher when the follow-up period is longer.[24] Retention rates after at least 6 months of follow-up range from 68%, to as low as 30.6% in our study.[12,24] Pregnancy registries lack internal comparators and a population-based denominator, and are unable to deliver estimates of incidence or risk.

The practical challenges of achieving high enrollment and high levels of retention in pregnancy registries mean that their full potential as a prospective data collection tool is infrequently achieved. The use of 'big data' to investigate rare events in very large cohorts provides an alternative or complementary approach to inform safety of vaccines in pregnancy. Population-based databases that hold vaccination data or that can be linked to vaccination records can be a powerful tool, providing access to large sample sizes, specific cohorts of interest and control groups that allow estimation of both incidence and risk. A growing number of studies have used population-based databases to investigate associations between exposure to vaccines and adverse pregnancy outcomes including spontaneous abortion, other obstetric events, adverse birth outcomes and diseases of later childhood such as autism spectrum disorder.[25–28] Many of these databases allow mother-baby links to be made, and can be used to identify potential congenital disorders not identified at birth, which is difficult, if at all possible, using registries. Pregnancy registries typically follow infants after birth for 6 to 12 months, which also limits their capacity to study diseases of later childhood, in contrast with many databases where the longitudinal medical history of individuals can be tracked. However, as yet, database studies to investigate vaccine safety in women exposed during pregnancy have not been widespread in the post-approval setting, and are often considered ancillary to pregnancy registries.[29]

GSK's IIV pregnancy registry was established as part of the pharmacovigilance plan to investigate the effects of exposure to seasonal IIVs during pregnancy. The registry data presented here are limited by the number of pregnancies and outcomes which are not sufficient to reach reliable and definitive conclusions about the risk of IIV exposure during pregnancy or within 28 days of conception. Despite the limitations of the data, these results contribute to the body of evidence supporting that seasonal IIVs can be safely administered during pregnancy. The findings from this study are aligned with previously published data and should be confirmed using robust data sources, such as healthcare databases. Population-based databases can be used to investigate specific research questions and can be powerful alternative or complementary tools to pregnancy registries.

A plain language statement is provided in Figure 1.

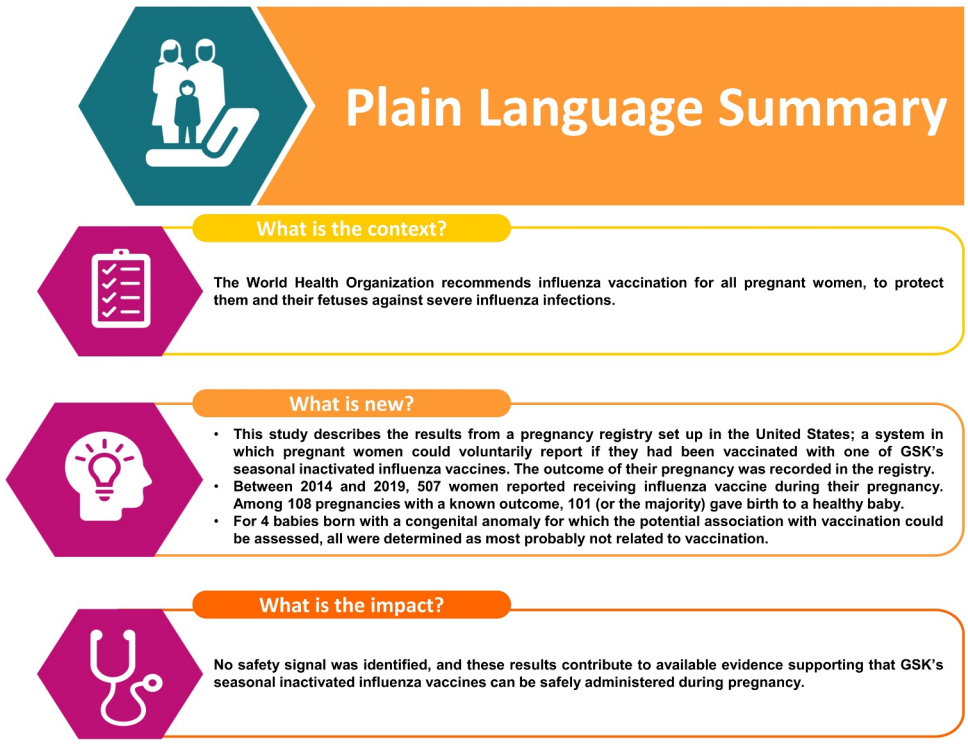

Figure 1. Plain language summary.

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Authors' contribution statement

Ugo Nwoji has made a substantial contribution to the study, drafting or reviewing the article critically for intellectual content and has approved the final version of the manuscript.

Disclosure of potential conflicts of interest

Ugo Nwoji is employed by and holds shares in the GSK group of companies. He declares no other financial or non-financial relationships and activities.

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Trademark statement

Fluarix, Fluarix Quadrivalent, FluLaval and *FluLaval Quadrivalent* are registered trademark owned by or licensed to the GSK group of companies.

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