

BMJ Open Passive enhanced safety surveillance of GSK's quadrivalent seasonal influenza vaccine in Belgium, Germany and Spain, an observational study: protocol for the 2018/2019 influenza season

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ABSTRACT

Introduction The European Medicines Agency requires Marketing Authorisation Holders providing seasonal influenza vaccines in Europe to conduct enhanced safety surveillance accounting for the different age groups based on the vaccine indication, in order to detect any potential increase of local and systemic adverse reactions early in an influenza season. To comply with this requirement, a multicountry European passive enhanced safety surveillance study has been set up to capture and assess adverse events occurring within 7 days following seasonal influenza vaccination. Here we share our surveillance protocol for the 2018/2019 influenza season.

Methods Nine healthcare professionals (HCPs) in Belgium, Germany and Spain have been recruited for this study. Cumulatively, approximately 1000 vaccinees will be provided with customised adverse event recording cards to report adverse events experienced within 7 days following vaccination with GSK's split-virion inactivated quadrivalent influenza vaccine. The cards are to be returned to the HCPs and the events encoded using an electronic case report form. Adverse event reporting rates will be analysed weekly and cumulatively, throughout the study period. Event rates will be described by country, age group and by influenza morbidity/mortality risk status of vaccinees (based on HCP assessment).

Ethics and dissemination Ethics committee approval was obtained for all participating sites prior to enrolment of the study participants. At the end of the study, each participating site will receive their data, and the outputs from the research will be made available to regulatory authorities. We intend to seek publication in peer-reviewed journals. GSK has posted a summary of the study protocol before the start of the study and results will be posted within 12 months of statistical analysis completion, in line with the National Institutes of Health recommendations.

Trial registration number NCT03688620.

INTRODUCTION

Influenza is a major public health burden with estimates of 290 000–650 000 respiratory deaths resulting globally each year from seasonal influenza outbreaks and epidemics.¹

Strengths and limitations of this study

- Three countries with different vaccination practices are included to enrol all age groups indicated for GSK's inactivated quadrivalent influenza vaccine and to account for diversity in terms of population characteristics.
- An electronic application is used to collect information in a standardised manner to facilitate the data extraction, cleaning and analysis; the aim being to maximise near real-time assessment.
- The sample size does not allow for the assessment of rare adverse events and other designs might be more appropriate for capturing such adverse events.
- Considering the passive nature of the setting, we cannot exclude under-reporting and potentially non-response bias, although this is expected to be limited with the visits scheduled.
- The age discrepancy between countries might result in different patterns of reporting.

Seasonal influenza causes 4–50 million symptomatic cases in the European Union (EU)/European Economic Area annually and between 15 000 and 70 000 European citizens die every year of causes associated with influenza.² Figures vary from season to season and according to the research methodology used.³ Annual vaccination is the most effective measure to reduce the risk of influenza infection and its complications.⁴ However, due to frequent genetic and antigenic changes in influenza viruses, seasonal vaccines are frequently reformulated with updated viral strains based on annual WHO recommendations.⁵ Therefore, there is a need for constant benefit–risk monitoring of these vaccines.

In the context of pharmacovigilance and continuous monitoring, the European Medicines Agency (EMA) released guidance on enhanced safety surveillance (ESS) for

seasonal influenza vaccines in the EU⁶ and thus replaced the request on the small-scale clinical trials for the evaluation of safety and immunogenicity of seasonal influenza vaccines required up to 2015.⁷ The guidance sets out standards for surveillance that all Marketing Authorisation Holders (MAHs) of vaccines in the EU must address. The key objective of the EMA ESS is to rapidly detect any significant increase in the frequency and/or severity of expected reactions (local, systemic or allergic reactions) that could indicate a potential safety concern requiring further investigation. From the EMA guidance we can read that *'it is not expected that the enhanced surveillance can exclude a change in reactogenicity or detect signals of rare events and therefore, as with any other medicine, the routine pharmacovigilance processes should be continued throughout the life-cycle of the product to ensure detection of any new, unexpected or rare risks'*.⁶ A recent review has discussed how several tools and routine surveillance activities could be used in addition to the ESS initiative to fulfil surveillance objectives.⁸

To implement the guidance appropriately, MAHs must first understand where their product(s) are to be distributed and administered (location/volume) and appreciate the disparities linked to local recommendations which may impact the subject population ultimately vaccinated. Specifically, for GSK's split-virion inactivated quadrivalent influenza vaccine (IIV4) 2018/2019 northern hemisphere influenza season, a feasibility assessment was conducted to identify which countries should be included in order to provide sufficient data (approximately 1000 vaccinees) with the objective to cover all age groups as per the GSK vaccine indications. The countries identified as suitable to host the study were: Belgium, Germany, and Spain where AlphaRix Tetra, Influsplit Tetra and Fluarix Tetra vaccines (three different trade names corresponding all to the GSK's IIV4) are distributed, respectively.

As opposed to active surveillance, no reminder or active follow-up of non-respondent subjects is performed. Subjects will be receiving their vaccination as per routine care prior to enrolment in the study. This passive ESS study is non-interventional and is designed to collect the appropriate safety information with the intent to capture in near real-time adverse events (AEs) experienced by vaccinees, in order to estimate the reporting rate of adverse events of interest (AEIs) experienced within 7 days following vaccination. To reach this objective customised AE reporting cards (AERCs) are to be completed by vaccinees or their parents/guardians after the receipt of their influenza vaccination. The cards are printed with predefined categories of AEIs to gather the most likely events to occur; along with an extra field to report any AE experienced that is not already listed as an AEI. Subsequent systematic coding of the information received by the vaccinees' healthcare practitioners is performed to standardise the data collection and analysis of AEIs.

This study protocol builds on the experience gained from other European passive ESS studies for seasonal influenza vaccines.⁹⁻¹⁶ MAHs have experimented with a number of different methodologies depending on the

countries where their products are distributed. Their aim is to find the right balance between the need to select countries implementing early vaccination campaigns (to rapidly detect any safety issues following introduction of a new vaccine formulation) and the need to enrol all age groups as per vaccine indication. Vaccine recommendations differ from country to country and some countries are well equipped for electronic database research with links between several sources of information enabling studies of large numbers of patients. For example, in England with many general practices using Electronic Health Records (EHRs), GSK gathered information of AEIs from EHRs in addition to enhancing reporting through the use of AERCs.^{11 16 17} However, nasal live attenuated influenza vaccine is preferentially recommended for children in England,^{18 19} and, although data were collected speedily, it was not possible to enrol a sufficient number of children to evaluate GSK's IIV4. The age representation was also a challenge encountered in a study conducted in Finland and the UK by another group, where vaccinees reported suspected adverse reactions via a telephone line with structured interview.¹³ This initiative was followed by a similar study in Ireland and the UK with an attempt to address the age group representation challenge.¹⁴

To date, there is no gold standard protocol for passive ESS. Certain methodologies may be better suited to specific countries and the countries recruited depend on where vaccine is used with sufficient market share to enable rapid collection of the required safety data. In conclusion, the study described in the reported protocol is intended to provide the necessary pharmacovigilance data as per requirement from the EMA guidance. Additionally, we anticipate that this study design and subsequent results may help inform decisions regarding future seasonal influenza vaccine safety surveillance studies in Europe.

METHODS AND ANALYSIS

Study setting and population

This prospective passive ESS study is anticipated to run from 1 October 2018 to 15 January 2019, with subject recruitment planned between 1 October 2018 and 31 December 2018 for subjects requiring one dose of vaccine. For subjects requiring two doses (namely those under 9 years of age who have not been previously vaccinated against influenza and therefore require two doses administered 4 weeks apart), the recruitment will stop at 1 December 2018 to allow sufficient time for follow-up. Nine healthcare professionals (HCPs) across Belgium, Germany and Spain will recruit approximately 1000 subjects. Due to feasibility constraints, Belgium and Germany, where vaccine coverage in children is low, will only recruit subjects 18 years of age and above (with German participating sites targeting subjects aged from 50 years onwards). Spain will target subjects between 6 months and 65 years of age at the time of the vaccination.

Written informed consent/informed assent will be collected as part of the study procedures subsequent to subjects receiving GSK's IIV4 according to the local guidelines²⁰ (see online supplementary file). Children in care will be excluded from the study (defined as children under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation).

Sample size considerations

The [table 1](#) shows the probability to observe at least one AE, the exact 95% CIs²¹ for the percentage of vaccinated subjects with the AE and relative SEs (RSEs) for a range of scenarios in terms of number of vaccinated subjects and true percentage of vaccinated subjects with the AE. Of note, a SE measure indicates the extent to which estimates derived from sample population surveys are likely to differ from data that would have been obtained from the overall population and is expressed as a number. The RSE is the SE divided by the estimate, usually expressed as a percentage. The larger the RSE, the less precise the survey estimate is of the true value in the population (estimates greater than 25%–30% should be used with caution).^{22 23} With an overall sample size of 1000 vaccinated subjects expected to be achieved by the end of the study period and a true percentage of vaccinated subjects with the AE ranging from 1% to 10%, the corresponding probability to observe at least one vaccinated subject with the AE is >99% and the RSE ranges from 9.5% to 31.5%.

The [table 2](#) shows the evolution by week of the cumulative probability to observe at least one AE, the exact 95% CI for the cumulative percentage of vaccinated subjects with the AE and RSE in the course of the study for an overall sample size of 1000 ((all countries) and 333 (by country)) vaccinated subjects and assuming an average percentage of vaccinated subjects experiencing an AE of 1%. The aim of computing these probabilities is to estimate what AE can be detected in the study with the study sample size. With a sample size of 1000 subjects, the study could detect very common ($\geq 10\%$), common ($\geq 1\%$ to $< 10\%$) and uncommon ($\geq 0.1\%$ to $< 1\%$) AEs and other AEs.

Data collection and analysis

Before the start of the study, participating HCPs will receive induction training to acquire certification that allows access to the application that will be used to encode the subjects' information. HCPs will then provide each vaccinee or their parent/guardian with a customised AERC (see [figure 1](#)) for the recording of any AE in the 7 days following the first and second vaccination (if appropriate). The cards will contain predefined AEs to be reported as well as a free text field to report any other AEs experienced by the subjects. Subjects will also have the possibility to indicate that no AE occurred within the 7 days' time window. The subjects are to return the cards to the HCP, and practice staff will enter the information

in an electronic case report form (eCRF). The AEs are to be entered according to the code list provided to each practice (see [figure 2](#)), in which AEs are coded according to the Medical Dictionary for Regulatory Activities (MedDRA) classification²⁴ and the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10).²⁵

The [table 3](#) provides the detailed schema for study procedures and completion of the eCRFs at the corresponding study visits. The procedures include, informed consent, collection of basic demography data ((month and year of birth (year only in Germany), geographic ancestry (Black or African American, Asian—central/south Asian heritage, Asian—east Asian heritage, Asian—south east Asian heritage, White—Arabic/north African heritage, White—Caucasian/European heritage, other), gender) and information on the vaccination—namely date of vaccination, batch number and any vaccine co-administrations. Investigators are also required to record, according to their experience and judgement, the 'risk status' of the vaccinee—either at risk or not at an elevated risk for influenza related morbidity and mortality. Some guidance was provided based on the risk groups usually recommended for vaccination in the EU. These usually encompass but are not limited to: pregnant women in some countries; children 6–59 months; individuals over 6 months with chronic heart or lung disease, metabolic or renal disease, chronic liver disease, chronic neurological conditions or immunodeficiencies; residents of long-term care facilities for older or disabled persons; healthcare workers including those who work in facilities that care for the elderly or those with disabilities. The risk status is collected to account for potential differences in healthcare seeking behaviours that could impact the probability of reporting any AE experienced.

The primary objective of the study is to estimate, in each country and overall, the cumulative percentages of subjects reporting AEs and/or other AEs, using AERCs, within 7 days following vaccination with GSK's IIV4. For each vaccinee (note that a second dose of GSK's IIV4 is planned to be administered only to children aged <9 years who have not previously been vaccinated against influenza in preceding seasons), the cumulative percentages of subjects reporting AEs and/or other AEs within 7 days postvaccination period (ie, the day of vaccination and the following 6 days) using AERCs from study start up to each study week (International Standardisation Organisation weeks 40–52) will be estimated by MedDRA preferred term, overall and by country; the denominator being the number of subjects vaccinated with GSK's IIV4 (and provided with an AERC) at any point from study start (ie, 1 October 2018) up to the end of the week of interest, in each country or for all countries and the numerator being the number of subjects from the denominator who reported the AE on the AERC within 7 days following vaccination. The 95% CI will be computed on all estimated percentages.

The secondary objectives are to estimate, in each country and overall, the weekly percentages of subjects reporting

Table 1 Probability to observe at least one AE, with the associated exact 95% CI and corresponding RSE according to number of vaccinated subjects and true percentage of vaccinated subjects with the AE

Number of vaccinated subjects	True percentage of vaccinated subjects with the AE (%)	Probability* to observe ≥1 vaccinated subject with the AE (%)	Number of vaccinated subjects with the AE	Exact 95% CI† on the percentage of vaccinated subjects with the AE		Associated RSE (%)
				Lower limit	Upper limit	
1500 (whole study period, all countries)	10	>99	150	8.53	11.63	7.7
	8	>99	120	6.68	9.49	8.8
	6	>99	90	4.85	7.32	10.2
	4	>99	60	3.07	5.12	12.6
	2	>99	30	1.35	2.84	18.1
	1	>99	15	0.56	1.64	25.7
	0.5	>99	7.5	0.21	1.00	36.4
	0.1	77.7	1.5	0.01	0.43	81.6
1000 (whole study period, all countries)	10	>99	100	8.21	12.03	9.5
	8	>99	80	6.39	9.86	10.7
	6	>99	60	4.61	7.66	12.5
	4	>99	40	2.87	5.41	15.5
	2	>99	20	1.23	3.07	22.1
	1	>99	10	0.48	1.83	31.5
	0.5	>99	5	0.16	1.16	44.6
	0.1	63.2	1	0.00	0.56	99.9
75 (per week, all countries)	10	>99	7.5	4.27	19.12	34.6
	8	>99	6	2.99	16.60	39.2
	6	99.0	4.5	1.83	13.99	45.7
	4	95.3	3	0.83	11.25	56.6
	2	78.0	1.5	0.14	8.28	80.8
	1	52.9	0.75	0.01	6.65	114.9
500 (whole study period, by country)	10	>99	50	7.51	12.97	13.4
	8	>99	40	5.78	10.73	15.2
	6	>99	30	4.08	8.45	17.7
	4	>99	20	2.46	6.11	21.9
	2	>99	10	0.96	3.65	31.3
	1	>99	5	0.33	2.32	44.5
	0.5	91.8	2.5	0.08	1.59	63.1
	0.1	39.4	0.5	0.00	0.93	141.4

Continued

Table 1 Continued

Number of vaccinated subjects	True percentage of vaccinated subjects with the AE (%)	Probability* to observe ≥ 1 vaccinated subject with the AE (%)	Number of vaccinated subjects with the AE	Exact 95% CI† on the percentage of vaccinated subjects with the AE		Associated RSE (%)
				Lower limit	Upper limit	
333 (whole study period, by country)	10	>99	33.3	7.00	13.74	16.4
	8	>99	26.6	5.32	11.45	18.6
	6	>99	20	3.70	9.12	21.7
	4	>99	13.3	2.17	6.70	26.8
	2	>99	6.7	0.79	4.15	38.4
	1	96.5	3.3	0.23	2.76	54.5
	0.5	81.2	1.7	0.04	1.99	77.3
	0.1	28.3	0.3	0.00	1.30	173.2
25 (per week, by country)	10	92.8	2.5	1.70	28.67	60.0
	8	87.6	2	0.98	26.03	67.8
	6	78.7	1.5	0.44	23.27	79.2
	4	64.0	1	0.10	20.35	98.0
	2	39.7	0.5	0.00	17.21	140.0
	1	22.2	0.25	0.00	15.52	199.0

*Binomial distribution.

†Clopper, Pearson.

AE, adverse event; RSE, relative SE.

Table 2 Cumulative probability to observe at least one AE, with the associated exact 95%CI and corresponding RSE by week for a true percentage of subjects with the AE of 1%

Number of vaccinated subjects	ISO weeks	Cumulative number of vaccinated subjects	Cumulative probability* to observe ≥ 1 vaccinated subject with the AE (%)	Cumulative number of vaccinated subjects with the AE	Average percentage of vaccinated subjects with the AE (%)	Exact 95% CI† on the cumulative percentage of vaccinated subjects with the AE		Associated RSE (%)
						Lower Limit	Upper limit	
1000 (whole study period, all countries)	40–40	75	52.9	0	1.00	0.00	4.80	114.9
	40–41	150	77.9	1	1.00	0.02	3.66	81.2
	40–42	225	89.6	2	1.00	0.11	3.17	66.3
	40–43	300	95.1	3	1.00	0.21	2.89	57.4
	40–44	375	97.7	3	1.00	0.17	2.32	51.4
	40–45	450	98.9	4	1.00	0.24	2.26	46.9
	40–46	525	>99	5	1.00	0.31	2.21	43.4
	40–47	600	>99	6	1.00	0.37	2.16	40.6
	40–48	675	>99	6	1.00	0.33	1.92	38.3
	40–49	750	>99	7	1.00	0.38	1.91	36.3
	40–50	825	>99	8	1.00	0.42	1.90	34.6
	40–51	900	>99	9	1.00	0.46	1.89	33.2
	40–52	1000	>99	10	1.00	0.48	1.83	31.5
333 (whole study period, by country)	40–40	25	22.2	0	1.00	0.00	13.72	199.0
	40–41	50	39.5	0	1.00	0.00	7.11	140.7
	40–42	75	52.9	0	1.00	0.00	4.80	114.9
	40–43	100	63.4	1	1.00	0.03	5.45	99.5
	40–44	125	71.5	1	1.00	0.02	4.38	89.0
	40–45	150	77.9	1	1.00	0.02	3.66	81.2
	40–46	175	82.8	1	1.00	0.01	3.14	75.2
	40–47	200	86.6	2	1.00	0.12	3.57	70.4
	40–48	225	89.6	2	1.00	0.11	3.18	66.3
	40–49	250	91.9	2	1.00	0.10	2.86	62.9
	40–50	275	93.7	2	1.00	0.09	2.61	60.0
	40–51	300	95.1	3	1.00	0.21	2.89	57.4
	40–52	333	96.5	3	1.00	0.19	2.61	54.5

*Binomial distribution.

†Clopper, Pearson.

AE, adverse event; ISO, International Standardisation Organisation; RSE, relative SE.

CONFIDENTIAL
Subject Number:

Enhanced safety surveillance of GSK's quadrivalent seasonal influenza vaccine

This surveillance is designed to capture adverse events following immunisation. Please report if you get any adverse event experienced following your influenza (flu) vaccination.

1. About you / About the person vaccinated

Date of Birth / (mm/yyyy) Male Female

2. When/where the flu vaccine was administered?

What date were you vaccinated / was the vaccine given? / /2018

Who administered the vaccine? a Healthcare Professional: Yes No

If no, please say who administered the vaccine : _____

3. Please report any symptoms/conditions in the 7 days after the flu vaccine (i.e., the day of vaccination and the following 6 days)

Please look at the list of possible adverse events following vaccination on the next page. Please tick the box and indicate the start date for any adverse event you/the person vaccinated experienced.

Please return the card in the envelope provided to your healthcare professional or study medical staff. Please return by post or in person.

Thank you for your help

4. If there were no symptoms experienced in the 7 days after vaccination (i.e., the day of vaccination and the following 6 days), tick and return

I have NOT/the person vaccinated has NOT experienced any adverse event following vaccination:

Please return the card in the envelope provided to your healthcare professional or study medical staff. Please return by post or in person.

Thank you for your help

Formal study name:
Passive enhanced safety surveillance of GSK's quadrivalent seasonal influenza vaccines: a pilot study in Belgium, Germany and Spain during the 2018/19 influenza season

GSK study abbreviation:
EPI-FLU 056 VS EU

Contact:
XXXXXX

CONFIDENTIAL
Subject Number:

Enhanced safety surveillance of GSK's quadrivalent seasonal influenza vaccine

Symptoms or reactions you experienced in the 7 days (i.e., the day of vaccination and the following 6 days) after your influenza vaccination	Please tick if you experienced the symptom	Start date of the symptom dd/mm/yyyy
Irritated or red eyes	<input type="checkbox"/>	_/_/_
Runny nose	<input type="checkbox"/>	_/_/_
Blocked nose	<input type="checkbox"/>	_/_/_
Nose bleed	<input type="checkbox"/>	_/_/_
Common cold	<input type="checkbox"/>	_/_/_
Cough	<input type="checkbox"/>	_/_/_
Sore throat	<input type="checkbox"/>	_/_/_
Hoarse voice	<input type="checkbox"/>	_/_/_
Wheezing	<input type="checkbox"/>	_/_/_
Loss of appetite	<input type="checkbox"/>	_/_/_
Nausea – feeling sick to your stomach	<input type="checkbox"/>	_/_/_
Vomiting – being sick to your stomach	<input type="checkbox"/>	_/_/_
Diarrhoea	<input type="checkbox"/>	_/_/_
Fever (temperature >38°C)	<input type="checkbox"/>	_/_/_
Allergic reaction (rash, itchy skin and/or eyes, runny nose)	<input type="checkbox"/>	_/_/_
Severe allergic reaction (Rash, difficulty breathing, dizziness, fast heart rate, swelling of lips/tongue)	<input type="checkbox"/>	_/_/_
Swelling of the face	<input type="checkbox"/>	_/_/_
Rash in a restricted part of the body	<input type="checkbox"/>	_/_/_
Rash all over body	<input type="checkbox"/>	_/_/_
Feeling irritable	<input type="checkbox"/>	_/_/_
Feeling tired	<input type="checkbox"/>	_/_/_
Headache	<input type="checkbox"/>	_/_/_
Shivering or feeling shaky	<input type="checkbox"/>	_/_/_
Seizure / fits	<input type="checkbox"/>	_/_/_
Muscle aches	<input type="checkbox"/>	_/_/_
Joint pain	<input type="checkbox"/>	_/_/_
Redness around injection site	<input type="checkbox"/>	_/_/_
Swelling around injection site	<input type="checkbox"/>	_/_/_
Pain at the injection site	<input type="checkbox"/>	_/_/_
Other	<input type="checkbox"/>	_/_/_
1. _____	<input type="checkbox"/>	_/_/_
2. _____	<input type="checkbox"/>	_/_/_
3. _____	<input type="checkbox"/>	_/_/_

Figure 1 Adverse event reporting card.

AEIs and/or other AEs using AERCs, within 7 days following vaccination with GSK's IIV4 overall, by age strata (6 months to 17 years; 18–65 years; >65 years) and risk status (at risk/not at risk) and the cumulative percentages (as detailed above) by age strata and risk status.

Data management procedure

A validated GSK-defined electronic data base application will be used to collect the data. Subject initials will not be collected or transmitted to GSK. Relevant data necessary for analysis and reporting will be entered/transmitted into a validated and secured database or data system using an audit trail system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures. GSK standards are based on the Clinical Data Interchange Standards Consortium.²⁶ While completed eCRFs are reviewed by GSK site monitors using a risk-based monitoring approach,²⁷ omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified member of site staff.

Routine pharmacovigilance procedures and safety reporting

The routine reporting of AEs/serious adverse events (SAEs) to regulatory bodies according to local routine practices will continue throughout the study period. Although the data collected for this study are primarily safety related, the reporting mechanisms for AEs/SAEs to regulatory authorities should not be altered and should continue according to

local standards. (SAEs considered related to the vaccine will be collected as part of the study using the eCRF.)

The investigator or site staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an AE of specific interest or an SAE as provided in this protocol.

An AE is any untoward medical occurrence in a subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product or temporally associated with a study procedure.²⁸

A SAE is any untoward medical occurrence that:

- a. Results in death.
- b. Is life-threatening.
- c. Requires hospitalisation or prolongation of an existing hospitalisation.
- d. Results in disability/incapacity.
- e. Is a congenital anomaly/birth defect in the offspring of a study subject.

If the participating HCP becomes aware of an SAE experienced by a study participant occurring within 7 days postvaccination that is deemed to be related to GSK's quadrivalent seasonal influenza vaccine according to the judgement of the HCP, the SAE should be reported to GSK within 24 hours of becoming aware using the eCRF.

Patient and public involvement

Patients or the public were not involved in the design of this study.

Project title: Passive enhanced safety surveillance of GSK's quadrivalent seasonal influenza vaccines: a pilot study in Belgium, Germany and Spain during the 2018/19 influenza season

Preferred code list

If a patient presents with adverse events within 7 days following vaccination (i.e., the day of vaccination and the following 6 days), please code (ideally as a symptom) any of the following events into their computerised record

Pre-defined AElS	MedDRA PT Terms	ICD-10 Codes	Notes	Pre-defined AElS	MedDRA PT Terms	ICD-10 Codes	Notes
Respiratory/Miscellaneous				General non-specific symptoms			
Conjunctivitis	Conjunctivitis (10010741)	H10.9	Irritated or red eyes	Irritability	Irritability (10022998)	R68.12 (Fussy baby)	Feeling irritable
Rhinorrhoea	Rhinorrhoea (10039101)	J34.89	Runny nose			R45.4 (Irritability and anger)	
Nasal congestion	Nasal congestion (10028735)	R09.81	Blocked nose	Fatigue	Fatigue (10016256)		Feeling tired
Epistaxis	Epistaxis (10015090)	R04.0	Nose bleed	Headache	Headache (10019211)	R51	Headache
Coryza	Rhinitis (10039083)	J00	Common cold	Neurological			
Cough	Cough (10011224)	R05	Cough	Bell's palsy	Facial paralysis (10016062)	G51.0	
Oropharyngeal pain	Oropharyngeal pain (10068319)	J02.9	Sore throat	Peripheral tremor	Chills (10008531)	R68.83	Shivering/ chills
Hoarseness	Dysphonia (10013952)	R49.0	Hoarse voice	Guillain-Barré Syndrome (GBS)	Guillain-Barré syndrome (10018767)	G61.0	
Wheezing	Wheezing (10047924)	R06.2	Wheezing	Seizure/Febrile convulsions	Febrile convulsion (10016284)	R56.0	Seizure/ fits
Gastrointestinal				Musculoskeletal			
Decreased appetite	Decreased appetite (10061428)	R63.0	Loss of appetite	Muscle aches/ Myalgia	Myalgia (10028411)	M79.1	Muscle aches
Nausea	Nausea (10028813)	R11.0	Feeling sick	Arthropathy	Arthropathy (10003285)	M25.9, M19.9	Joint pain
Vomiting	Vomiting (10047700)	R11.10	Being sick	Local Symptoms			
Diarrhoea	Diarrhoea (10012735)	R19.7	Diarrhea	Local erythema	Injection site erythema (10022061)	T50.B95	Redness around the injection site
Fever/Pyrexia				Local swelling	Injection site swelling (10053425)	T50.B95	Swelling around the injection site
Fever	Pyrexia (10037660)	R50.9	Temperature >38°C	Local pain	Injection site pain (10022086)	T50.B95	Pain at the injection site
Sensitivity/Anaphylaxis				If a patient hands back the AERC with their symptoms – please code these and report it in the eCRF			
Hypersensitivity reaction	Hypersensitivity (10020751)	T78.4	Allergic reaction				
Anaphylactic reaction	Anaphylactic reaction (10002198)	T78.2	Severe allergic reaction				
Facial oedema	Face oedema (10016029)	R60.0	Swelling of the face				
Rash							
Rash	Rash (10037844)	L27.1	Rash in a restricted part of the body				
Generalised rash	Rash generalised (10037858)	L27.0	Rash all over body				

N.B.: In coding these conditions there is **no assumption about causation**; this can only come from advanced analytics.

Principal Investigator: XXXX

Figure 2 Code list of prespecified AElS. AERC, adverse event reporting card; AElS, adverse events of interest; eCRF, electronic case report form; GBS, Guillain-Barré Syndrome; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th revision; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term.

Ethics and dissemination

The following Ethics Committees (ECs), or Institutional Review Boards (IRBs) and Regional Authorities were consulted in line with country requirements, namely, Commissie Medische Ethiek UZ/KU Leuven (EC) in Belgium (S61698; approval received 24 August);

Ethik-Kommission der Bayerischen (EC) in Germany (18056; approval received 20 September) and in Spain the PEIBA (IRB and RA combined) for Andalusia (0031/18 EPA-SP; approval received 26 September) and Hospital Vall de Hebron (IRB) and Goli Gurina (RA) for Catalonia (ID-RTF-021; approval received 22 October).

Table 3 Study procedures and prospective data collection

	Prospective data collection			
	Visit 1	Visit 2	Visit 3*	Visit 4*
	Day 1	Day 8	Day 29	Day 36
Visit number				
Time points				
Type of contact	Study visit Belgium, Germany, and Spain	Study visit or mailing† Belgium, Germany, and Spain	Study visit Spain	Study visit or mailing† Spain
Country				
Informed consent	●			
Check inclusion criteria	●			
Check exclusion criteria	●			
Collect demographic data	●			
Collect “at risk” status as per HCP assessment	●			
Record the vaccination data for GSK’s quadrivalent seasonal influenza vaccine	●		●	
Check and record co-administered vaccination	●		●	
Distribute AERCs	○		○	
Train subject/subject’s parent (or LAR) to complete AERC	○		○	
Subject/subject’s parent (or LAR) records postvaccination AEs and/or other AEs occurring within 7 days post vaccination	●	●	●	●
Subject/subject’s parent (or LAR) returns AERC†		○		○
Investigator or delegate transcribes data from AERC to eCRF		●		●
Record of vaccine-related SAEs occurring within 7 days post vaccination	●	●	●	●
Study conclusion		●‡		●

● Is used to indicate a study procedure that requires documentation in the individual eCRF.

○ Is used to indicate a study procedure that does not require documentation in the individual eCRF.

*Only applicable for children aged <9 years who have not previously been vaccinated against seasonal influenza and to whom a second dose should be given after an interval of at least 4 weeks.

†Subject/subject’s parent (or LAR) returns AERC either in person during a study visit or by mail, to the HCP (or a member of his/her team).

‡Not applicable for children aged <9 years if they follow the recommendations of a two-dose schedule with 4 weeks interval.

AE, adverse event; AEI, adverse event of interest; AERC, adverse event reporting card; HCP, healthcare professional; LAR, legally acceptable representative; SAE, serious adverse event; eCRF, electronic case report form.

In the respective countries, the ethics approval preceded the study participant's enrolment, with the first subject enrolled at the earliest on 1 October 2018.

The outputs from the research will be disseminated primarily through peer reviewed journal articles and presented at relevant seminars and conferences. GSK will post the study protocol and the results summary within 12 months of statistical analysis completion (following review and comment by GSK) on GSK's Clinical Study Register (accessible at www.gsk-clinicalstudyregister.com, GSK Study ID 207737) and on the US National Library of Medicine website www.clinicaltrials.gov (NCT03688620). The study report will also be posted 30 days after the publication of the primary and main secondary endpoints. Additionally, at the end of the study, each participating site will receive their data.

Trademarks

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Contributors GDS led the development of the protocol and wrote the first draft of the manuscript. AY and VS provided critical contributions to safety sections. SD contributed to the statistical sections. EZ-v-D contributed to the data management section, KS for study operational aspects and FL coordinated the protocol writing. AS provided critical contributions to the clinical and epidemiology sections. All authors contributed to subsequent revisions and approved the final version.

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Competing interests VS declares he is employed by VPN Consultancy Limited working on behalf of the GSK group of companies. KS declares she is employed by Syneos Health working on behalf of the GSK group of companies. FL declares he is employed by 4Clinics Belgium working on behalf of the GSK group of companies. AS reports he was employed by the GSK group of companies at the time of the study and reports he holds shares in the GSK group of companies. EZ-v-D declares she is employed by the GSK group of companies. AY, GDS and SD declare they are employed by the GSK group of companies and hold shares in the GSK group of companies.

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