In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

The following guiding principles have been applied to the disclosure:

- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- *Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*
- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

Enhanced safety surveillance (ESS) of seasonal influenza vaccines: feasibility study

[redacted]

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List of abbreviations

ABE	Audit-based education
AEI	Adverse event of interest
CCG	Clinical Commissioning Group
CMO	Chief Medical Officer
CRN	Clinical Research Network
CTV3	Clinical Terms Read version 3
[redacted]	[redacted]
ECDC	European Centre for Disease Prevention and Control
EHR	Electronic Health Record
EMA	European Medicines Agency
EMIS	Egton Medical Information Systems
GSK	GlaxoSmithKline
GP	General Practitioner
HES	Hospital Episode Statistics
HSCIC	Health and Social Care Information Centre
IDE	Illness-disorder episode
IMD	Index of Multiple Deprivation
INPS	In Practice Systems
LSOA	Lower Super Output Area
MHRA	Medicines and Healthcare Products Regulatory Agency
MIQUEST	Morbidity Query Information Export Syntax
NIHR	National Institute for Health Research
ONS	Office for National Statistics
OR	Odds ratio
PHE	Public Health England
QOF	Quality Outcomes Framework
[redacted]	[redacted]
REC	Research Ethics Committee
SOAP	Simple Object Access Protocol
SLA	Service Level Agreement
TPP	The Phoenix Partnership

1. Extended Abstract

Background

The European Medicines Agency (EMA) have proposed that a list of possible adverse events of interest (AEIs) should be subject to surveillance at the start of influenza vaccination season. UK primary care has a registration-based systems, practitioners administer most flu vaccine, all routine clinical work is carried on using electronic health records (EHR) and technologies exist to pool data in near real time.

Objective

To demonstrate the feasibility of weekly estimation of vaccine coverage, by age strata and by vaccine brand and weekly reporting of AEI rates; comparing GSK vaccine with other brands.

Method

We recruited nine volunteer general practices, who had already selected their brand of flu vaccine for the 2015/2016 winter season. These were divided into three who joined an EMA defined "enhanced surveillance (ES)" arm – this involved every patient vaccinated receiving a Yellow adverse reaction card; these cards were returned to the practice and entered into the patient's EHR. Two of these practices used GSK brand of vaccine. All of the practices had EHR data mining (EHR-DM). Data were extracted weekly remotely, with a fall back of manual data extraction, which had to be implemented in two practices. Whilst the ES practices also had EHR data mining (n=3), we reserved the title EHR data mining to the practices that had EHR data mining only (n=6).

The data were processed into a real time weekly report that compared ES with EHR-DM, and GSK with non-GSK vaccine; between weeks 35 and 49. We also reported AEIs (though in the non-immunised we called them "illness-disease episodes (IDE)" in the non-vaccinated to provide an indication of background rates and as a signal seen in IDE and AEI is unlikely to have a vaccine related aetiology (we use the term "signal" to mean any change in data that leads us to form a hypothesis about possible causal relationship with vaccine exposure).

We compared the weekly surveillance reports – there are weekly cross-sections extracted in real time – with a retrospective cohort of patients registered 6 weeks after the end of the observation period. We looked at the rates of AEI/IDE in this group compared with those reported in the surveillance/weekly cross-sectional reports. We also looked at hospitalisation, and level of fever as markers of severity. We compared the odds ratios of an adverse event between GSK and non-GSK practices; conducted a logistic regression of what predicts an AEI/IDE and an analysis adjusting for propensity to be vaccinated.

Feasibility analysis involved a comparison with [redacted] methods to ensure timeliness, completeness and accuracy. We used comparison with the reported uptake and coverage of influenza vaccine and recording of AEI/IDE within the [redacted] as a surrogate for data quality in this study.

Results:

Population:

The cross sectional (weekly surveillance) population was larger (N=80,635 (week 49) vs. cohort N=71,407) and younger: especially age 20-24years, had a greater proportion of males, was

more deprived but no different in ethnicity. Our practices were well distributed, but lacked an inner city practice, were less deprived and ethnically mixed than the National average.

Vaccine exposure

More people were vaccinated in the serial cross-sectional study (n=22.1% ,n=15,791) vs. cohort 20.7% (n=14.801)). 4.75% (n=163) and 7.28% (n=827) more people were observed as vaccine exposed to the GSK and non-GSK vaccine; an extra 1.4% (n=990).

Adverse events following immunisation (AEI):

The rates of AEIs in non-GSK brand vaccine 14 day post vaccine AEI compared with the GSK vaccine were 3.00% (95% CI 2.71%-3.30%) and 2.61% (95% CI 2.11%-3.14), respectively in the weekly cross-sections. In the cohort analysis the equivalent rates were: 14 day post vaccine AEI; 2.68% (95% CI 2.15%-3.23%) compared with 2.93% (95% CI 2.62%-3.25).

In the 14-day observation window post vaccination the commonest AEIs presenting were respiratory, fever and musculoskeletal. Respiratory 0.96% (95%CI 0.79%-1.14%, n=117) for non-GSK compared with 0.89% (95%CI 0.58%-1.20% n=32) for GSK vaccine; fever 0.8% (95%CI 0.64%-0.96%, n=97) for non-GSK and 0.65% (n=24) for GSK; and for musculoskeletal conditions 0.52% (95%CI 0.39%-0.65%, n=63) and 0.89% (95%CI 0.58%-1.20%, n=32).

Similar proportions but with different rates were seen in the cohort analysis.

The rate of reporting from yellow cards was 1.2% (52/6776); however their use was associated with more reporting of local side effects.

The EMA listed AEIs (we describe them as IDE in non-vaccinated) are common among the non-vaccinated population. Over the 15 week observation period the rate of AEI/IDEs in the cohort analysis was 11.9% (95%CI 11.38%-12.42%) for those vaccinated (this included any period before as well as after vaccination) and 5.19% (95%CI 5.01%-5.35%) in the non-vaccinated.

Hospital admission associated with AEI

Cohort data analysis shows 2.2% (n=2; 95%CI 2.2%-3.3%) of people vaccinated with GSK flu vaccine were admitted to hospital concurrent with an AEI in the 14 days following vaccination; compared with 3.9% (n=13; 95%CI 1.8%-2.1%) in the non-GSK vaccinated group.

Statistical analysis

Crude odds ratios of an AEI were no different for GSK and non-GSK brands of vaccine in the 14 day period post vaccination; OR 0.91 (95%CI 0.72%-1.15%; p=0.44). There was some difference in individual types of AEI showing the feasibility of these analyses, though the study is not designed to detect differences.

The comparison using multivariate logistic regression between GSK vs. non-GSK in the 14 day post vaccination window showed some differences, but the unequal distribution of observation may account for this. Male gender is associated with lower levels of AE recording; the OR is 0.68 (95%CI 0.55-0.83; p<0.001). Groups less likely to attend could be targeted using yellow cards or other direct methods of approach.

The propensity matched (n=7,562) patients (vaccinated with non-vaccinated) showed those vaccinated had a greater OR of reporting AEIs/IDEs than those who had not been vaccinated OR 4.34 (95%CI 3.83-4.93).

Feasibility analysis

Feasibility analysis showed: (1) Timeliness was comparable with [redacted] Data were extracted each week with two practices requiring local extracts (carried out exceptionally because of the small size of this pilot); (2) Completeness of data for morbidity and vaccination was at high level. The [redacted] rate of overall influenza vaccine update is 20.2%, the overall rate of these 9 practices is 20.7%. (3) Accuracy of the data was comparable with that available in [redacted] comparing these data with rates generated for the same weeks in 2014 from >100 practices.

Conclusions

We demonstrated that we can create a weekly report of brand specific vaccine coverage and EMA specified AEI from routine primary care data. We did this in a timely way reporting the previous week's data during the following week. The reports show that AEI rates post vaccination are around 3%. Enhanced passive surveillance using a yellow card scheme improved recording of some AEIs notably local reactions. The yellow card scheme could be targeted on those who attend less and report less AEIs – notably men.

The comparison with the [redacted] data suggests our extraction and data are complete and accurate.

Background rates of AEI/IDE are useful as these conditions are common and a rise in AEI associated with a rise in IDE is less likely to have a vaccine related aetiology.

Additional statistical techniques such as statistical process control or use of control charts might enhance the ability of the surveillance/repeated cross-sectional data to detect signal.

A retrospective cohort study, conducted mid or end of season can provide more definitive rates than repeated cross-sections where there is flux in the population. Those first registering may do so at a time when they are symptomatic. Longer term follow up allows capture of hospital or other longer term data with greater accuracy.

Recommendation

We recommend that for next season that yellow card enhanced (passive) surveillance is introduced in parallel with EHR-EM. The yellow cards should be targeted at groups less likely to report events (e.g. males). The weekly surveillance should be used to detect any signal with the cohort analysis providing definitive benchmark rates of AEIs.

2. Executive Summary

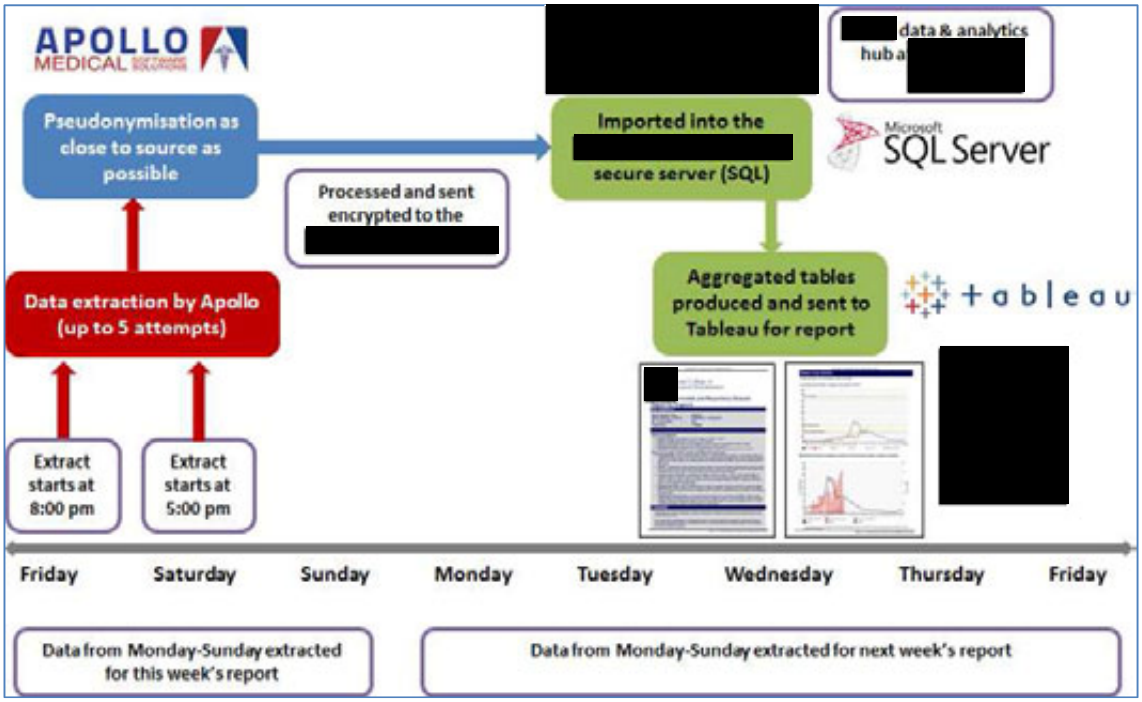
2.1. Background

The European Medicines Agency (EMA) has proposed that a list of possible adverse events of interest (AEIs) should be subject to brand specific surveillance in the first weeks after the start of influenza vaccination. The EMA defined three types of enhanced surveillance: Active (post authorisation surveillance); Enhanced passive; and Electronic health record (EHR) data mining.

UK general practice has a registration-based list system, which has been highly computerised since 2004 with consultation records created by family doctors in real time during the clinical consultation. UK general practice also administers most influenza vaccination and other immunisation programmes to all age-groups registered with that practice. This influenza vaccine is purchased by the practices each season. General practices are generally independent professional partnerships and make their own decision about which brand of influenza vaccine to purchase. Generally, they purchase a single vaccine for the practice prior to the start of the flu season.

UK general practice data have been used in disease surveillance for many years. Technologies developed in [redacted] and used in [redacted] allow the rapid processing and analyses of data collected from across the country for disease surveillance; they have potential to be used for rapid vaccine risk assessment. In the [redacted] data are extracted at the end of each week and processed by the end of the Wednesday of the following week, with a second data extraction conducted, but only used in times of pandemic (Figure 1).

Figure 1 – Schematic representation of the weekly cycle of data extracted from [redacted] practices at the end of each week and processed into the [redacted] weekly report



We carried out this study to test the feasibility of conducting EMA-defined enhanced passive surveillance and EHR data mining in UK general practice, comparing one brand of influenza vaccine (GSK brand) with others administered in primary care. Our study design set out to ascertain if enhanced passive surveillance, in this study giving vaccinated patients a yellow card, added anything to EHR data mining. Active surveillance, as defined by EMA, is beyond the scope of this study.

2.2. Objectives

The study objectives, as set out in the protocol were:

Primary objectives:

- Weekly estimation of vaccine coverage, by age, risk group, and by vaccine brand.
- Weekly reporting of AEI rates among subjects vaccinated against seasonal influenza, by age, co-morbidity, and brand from the GP practices using the EHR-data mining method, and those using the enhanced passive surveillance system.

We used a weekly cross-sectional report to provide the weekly reports (Appendix A). We subsequently carried out a retrospective cohort study to provide confirmed rates.

Secondary objectives:

- To assess the completeness of the vaccination data in the EHR-data mining and enhanced passive surveillance systems.
- To assess the timeliness of vaccination data in both surveillance systems
- To assess the completeness of AEI reporting in both surveillance systems
- To assess the timeliness of AEI reporting in both surveillance systems
- To assess whether the rates of the most frequently reported events are compatible with expectations from published rates in a comparable population.

2.3. Methods

2.3.1. Sample practices and data extraction

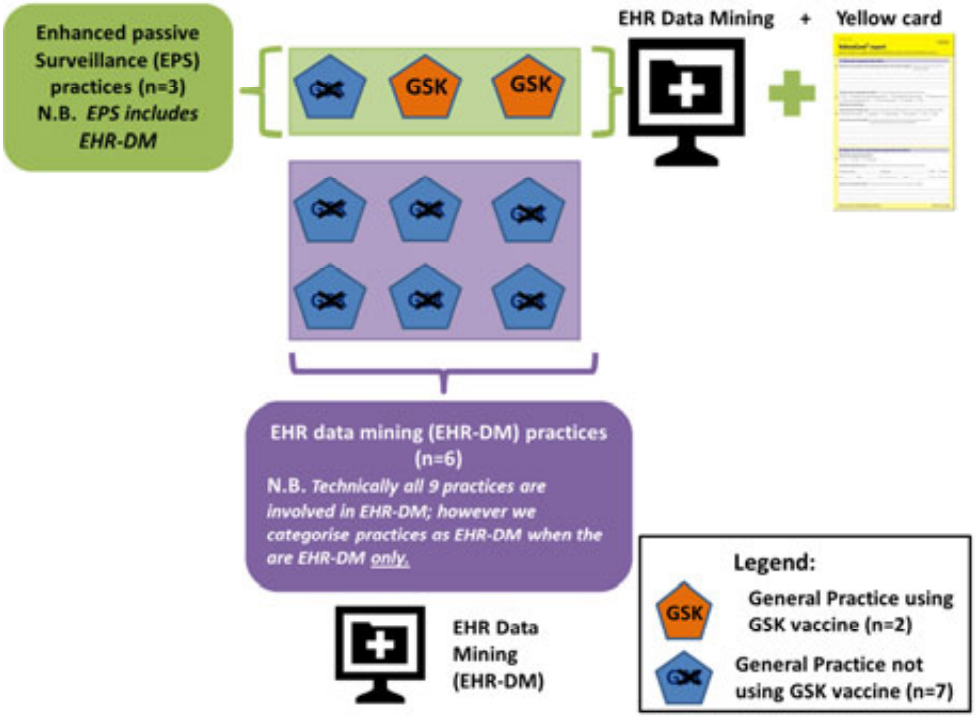
We planned to purposively sample and recruit nine practices spread across England, from varying types of locality and using different EHR systems. We planned to recruit them after they had selected their brand of vaccine for the coming influenza season (i.e. the study team would have no impact on the choice of influenza vaccine to be administered by a participating practice).

We developed code lists that would enable us to identify the EMA-listed AEIs within GP computer records (EHR data mining). Our queries would extract data to identify vaccinated patients and any AEI post-vaccination, and also to detect background rates of the same conditions in the non-vaccinated. We termed the same list of conditions "illness-disorder episodes" (IDE) when they occur in the non-vaccinated population. We grouped the individual AEI/IDE into broad categories, largely by body system, for ease of reporting. Our groups were: respiratory/miscellaneous, gastrointestinal, fever/pyrexia, sensitivity/anaphylaxis, rash, other

general symptoms, neurological, musculoskeletal and local to the vaccination. We adopted the same data extraction timing as we developed for [redacted]

We divided our practices into two groups. The first group included three practices participating in enhanced passive surveillance combined with EHR data mining. This enhanced passive surveillance group included the two GSK brand influenza vaccine using practices (Fig 2). The second group included six practices participating in EHR data mining alone. In the enhanced passive practices vaccinated subjects were given a yellow card to prompt them to report, or use the card to report any AEIs (Appendix D). The yellow card is an adverse drug reaction (ADR) card developed by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK for collecting information on suspected adverse reactions related to any healthcare products. However, rather than sending the card to a third party, the card was returned to the practice and coded into the practice EHR, making these conditions additive to those reported directly to the practice.

Figure 2 - Schematic representation of the distribution of the two GSK vaccine brand practices within the study, they were both within the enhanced passive surveillance arm (Yellow card and EHR data mining)



The rates of IDEs in non-vaccinated patients provided a background rate of IDE to compare with AEIs of the vaccinated group, as no historical background rates of AEIs were available. Information about the rate of IDEs (i.e. AEIs in the non-vaccinated) would also enable us to avoid misinterpreting a sudden rise in AEIs with a non-vaccine related aetiology, which might occur if we only observed vaccinated patients.

The data are extracted from GP computer systems using an established data extraction method designed at the [redacted] for the [redacted] The data are received pseudonymised and encrypted into a secure network. They are loaded into a SQL database, which links to a Tableau Software that can programmatically generate the weekly reports in less than an hour.

2.3.2. Weekly real-time cross-sectional reports

We extracted weekly cross-sectional data to report AEIs/IDEs on a week-by-week basis comparing AEIs in the vaccinated with IDEs in the non-vaccinated for a 15-week period (week 35 to week 49). We used a well-established remote data extract system, with the fall-back of a local practice level data extract, if needed. Because of delays in permissions and practices starting vaccinations earlier than anticipated our first feedback was in week 42 (Appendix B).

The weekly real time reports were a cross-sectional analysis using all registered patients as the denominator. The denominator varied each week as patients left and joined their practice. We describe the characteristics of the patients registered in the practices including age-sex profile, ethnicity, and deprivation score, for patients registered between weeks 35 and 49. We also report the rates of vaccine exposure, providing a record of the cumulative rate of vaccination and the total vaccinated in the GSK and non-GSK influenza vaccine utilising practices. We report the vaccination rates and AEI and IDE rates for week 49 as a cumulative record of that described in the weekly reports.

We constructed a report in the format we have developed for the [redacted] In this report we compare enhanced passive and EHR data mining surveillance graphically and in a tabular format and provide comparative data between GSK and non-GSK practices. Once a format of surveillance is selected we would use this report format to report the brand of interest compared with other brands.

2.3.3. Cohort analysis

We conducted a retrospective cohort analysis to compare the outputs generated in the weekly cross-sectional data. There is also an opportunity to check out the severity and sequelae of any AEIs. We repeat our report of the characteristics of the patients registered in the practices included in the study, their age-sex profile, ethnicity and deprivation score. We also reported the rates of vaccine exposure, providing a record of the cumulative rate of vaccination and the total vaccinated in the GSK and non-GSK influenza vaccine utilising practices.

We then set out the rates of AEI for the vaccinated patients, in the 14 days following vaccination. We compared rates of AEI reported for the GSK vaccine comparing those vaccinated with other brands of vaccine. We also provide for the whole 15-week observation period the rates of AEI/IDE for non-vaccinated compared with vaccinated patients.

To assess the feasibility of enhanced passive surveillance we report the number of yellow cards handed out to patients in the enhanced passive surveillance arm and the rate of return of these cards. We measured the severity of any AEI within the cohort population. We included data about: (1) Hospital Admissions and (2) the degree of pyrexia where reported in the EHR. We described the rate of hospital admissions, based on data in the GP record. We reported the rate of admissions concurrent with AEIs comparing GSK brand vaccinated with other brands of

vaccination within 14 days of vaccination, and also for admissions concurrent with AEIs at any time in the observation window. We report fever, where recorded.

We conducted additional statistical analysis of the cohort: (1) Reporting the crude odds ratios (OR) with 95% confidence intervals (95% CI) of an AEI/IDE group occurring; (2) Using multivariate logistic regression to report AEI/IDE, adjusting for age, gender, ethnicity, deprivation score, and high risk group; and (3) Propensity matching: matching vaccinated with non-vaccinated to see which variables were associated with AEI/IDE. We reported the crude ORs and the multivariate logistic regression making two comparisons:

1. We compared GSK with non-GSK influenza vaccine with AEIs within 14 days of vaccination as the outcome measure.
2. We compared vaccinated patients with non-vaccinated patients with AEI/IDE at any time during the observation period as the outcome measure.

With the exception of the factors included in our logistic regression and our propensity matching our analysis does not seek to match the populations, particularly where we make the comparison between vaccinated and non-vaccinated. The vaccinated groups will include those with a higher propensity to consult.

2.3.4. Comparison of real-time with the cohort analysis

We compared denominators and characteristics of the populations in the real-time repeated cross-sections with those in the cohort. We also reported the influenza vaccination exposure rates in these populations and made a descriptive comparison of any difference in the pattern of AEIs between GSK brand and non-GSK influenza vaccine and between AEIs in all the influenza-vaccinated compared with the rates of IDE in the non-vaccinated.

2.3.5. Feasibility indicators:

We reported on feasibility indicators that should inform which is the most appropriate method of enhanced surveillance. We assessed:

- Timeliness of vaccination data in the EHR
- Completeness of vaccination data in the EHR. We compared rates with [redacted]
- Timeliness of AEI reporting in the EHR and through yellow card reporting
- Completeness of AEI reporting in the EHR and through yellow card reporting
- The accuracy of the data. We compared the rates of AEI/IDE recorded in the [redacted] using data for the same weeks (35-49) in 2014.

2.3.6. Ethical approval:

The study was approved by an [redacted] proportionate review (REF: 15/LO/1254). The [redacted] approved the use of aggregated data to compare rates of vaccination and of background AEI/IDE recording.

2.4. Results

2.4.1. Sample practices and data extraction:

We were not able to be as selective in practice recruitment as intended, due to time pressures. The nine practices recruited had an age-sex distribution similar to the national average and were evenly distributed geographically, but less deprived and with a higher white ethnicity than the national population. All nine practices gave permission for EHR data mining, with three

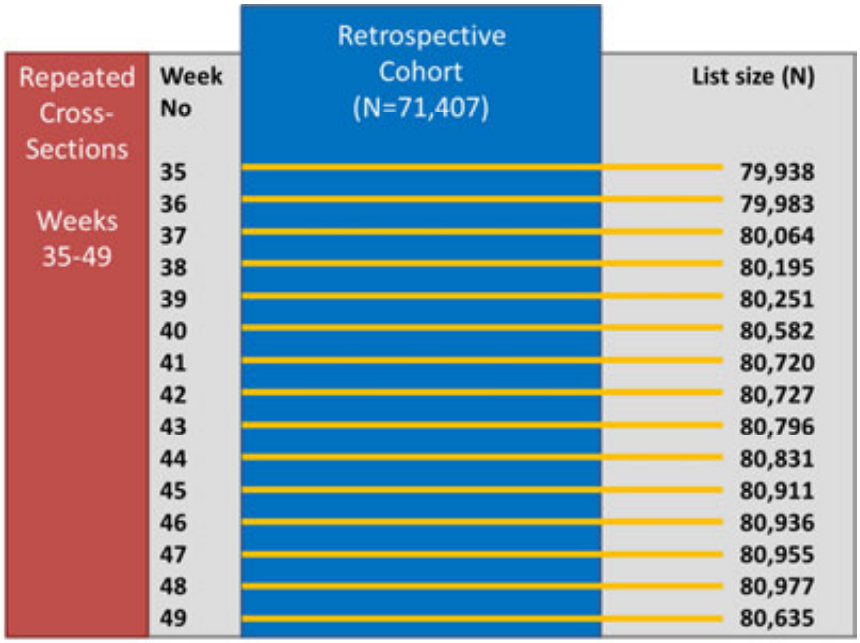
practices in addition taking part in enhanced passive surveillance, providing a yellow card to all those who were vaccinated. Two of the nine practices were GSK influenza vaccine practices; both of them were part of the enhanced passive surveillance arm.

2.4.2. Weekly real-time cross-sectional reports:

Most data were collected using a remote data extract system; some data from two practices had to be collected manually. We generated and published weekly AEI reports starting in week 42. For two practices weekly report data were incomplete and had to be collected using a local data extract tool.

The population in the cross-sectional study was 80,635 (we used the week 49 denominator) with a female:male ratio of 0.992:1. The proportion of the population above 50 years old and of people aged 20-24 years was above the national average. The population was less deprived with around three-quarters (72.3%) drawn from the 50% least deprived (Figure 3).

Figure 3 - Schematic representation to contrast the cohort population with the repeated cross sections



19.58% (n=15,791) of the population were vaccinated. The GSK practices vaccinated a higher proportion of their practice population. Rates of vaccine exposure collected in real time cumulative through to week 49 were: 23.3% (3,579/15,420) and 18.7% (12,194/65,215) for GSK and non-GSK vaccine practices respectively (Pearson Chi square $p<0.001$).

We showed no difference in the rates of AEIs when we compared non-GSK brand vaccine 14-day post vaccine AEI with the GSK vaccine: 3.00% (95% CI 2.71%-3.30%) compared with 2.61% (95% CI 2.11%-3.14), respectively. The EMA-listed AEIs (we describe them as IDE in non-vaccinated) are common among the non-vaccinated population. Over the 15-week observation period the rate of AEI/IDEs was 12.08% (95%CI 11.57%-12.59%) for those vaccinated (this included any period before as well as after vaccination) and 5.67% (95%CI 5.50%-5.85%) in the non-vaccinated.

In the 14-day observation window post vaccination the most common AEIs presenting were respiratory, fever, and musculoskeletal. Respiratory 0.96% (95%CI 0.79%-1.14%, n=117) for non-GSK compared with 0.89% (95%CI 0.58%-1.20% n=32) for GSK vaccine; fever 0.8% (95%CI 0.64%-0.96%, n=97) for non-GSK and 0.67% (95%CI 0.42%-0.95%, n=24) for GSK; and for musculoskeletal conditions 0.52% (95%CI 0.39%-0.65%, n=63) and 0.89% (95%CI 0.58%-1.20%, n=32). Similar proportions but with different rates were seen in the cohort analysis.

The background rates for respiratory in the vaccinated compared with the non-vaccinated over the 15-week observation period were: 4.49% (95% CI 4.17%-4.81%, n=709) and 1.92% (95%CI 1.82%-2.03%; n=1246). The equivalent results for fever/pyrexia are 3.08% (95% CI 2.82%-3.36%, n=487) and 1.55% (95%CI 1.45%- 1.64%, n=1003), and results for musculoskeletal are 2.39% (95%CI 2.16%-2.63%, n=378) and 0.92% (95%CI 0.85%-1.00%; n=598). All figures are quoted for non-GSK compared with GSK respectively.

2.4.3. Cohort analysis:

The population in the cohort study was 71,407 with a female:male ratio of 0.989:1. The proportion of the population above 50 years old was above the national average. 20.7% (n=14801) of the population were immunised. The rates of vaccine exposure were different between the GSK and non-GSK vaccine practices: 24.7% (3,434/13,891) vs. 19.8% (11,367/57,516) respectively, (Pearson Chi square $p<0.001$). The practices using the GSK vaccine immunised a high proportion of older people.

We showed no difference in the rates of AEIs when we compared the GSK vaccine with non-GSK brand vaccine 14-day post vaccine: 2.68% (95% CI 2.15%-3.23%) compared with 2.93% (95% CI 2.62%-3.25). The EMA-listed AEIs (we describe them as IDE in non-vaccinated) are common among the non-vaccinated population. Over the 15-week observation period the rate of AEI/IDEs was 11.9% (95%CI 11.38%-12.42%) for those vaccinated (this included any period before as well as after vaccination) and 5.19% (95%CI 5.01%-5.38%) in the non-vaccinated.

The three enhanced passive surveillance practices handed out yellow cards to 61% (4150/6776) of the vaccinated population. 2% (82/4150) of these cards were returned.

2.2% (n=2; 95%CI 0.0%-5.4%) of people vaccinated with GSK flu vaccine were admitted to hospital concurrent with an AEI in the 14 days following vaccination; compared with 3.9% (n=13; 95%CI 2.1%-6.0%) in the non-GSK vaccinated group. Over the whole 15-week observation period admissions of vaccinated people concurrent with an AEI/IDE were 2.5% (95%CI 1.8%-3.2%) across all vaccinated, compared with 1.0% (95%CI 0.7%-1.4%) in the non-vaccinated. Similar proportions of people presented in the 14 days post vaccine and had their temperature recorded numerically: 0.50% (95%CI 0.26%-0.73%) in those vaccinated with GSK brand and 0.63% (95%CI 0.49%-0.78%) in those vaccinated with other brands of flu vaccine. Background rates across the whole observation period were 2.66% (95%CI 2.40%-2.92%) for those vaccinated and 1.17% (95%CI 1.08%-1.26%) for subjects who were not.

Recorded rates of respiratory, fever/pyrexia, and musculoskeletal were as follows: 0.95% (95% CI 0.77%-1.13%) vs. 0.90% (95%CI 0.61%-1.22%) for respiratory; 0.77% (95%CI 0.61%-

0.93%) vs. 0.67% (0.41%-0.96%) for fever/pyrexia; and 0.48% (95%CI 0.35%-0.61%) vs. 0.93% (95%CI 0.61%-1.25%) for musculoskeletal.

Crude odds ratios of an AEI were no different for GSK and non-GSK brands of vaccine in the 14-day period post vaccination: OR 0.91 (95%CI 0.72%-1.15%; p=0.44). The only significant differences observed were less gastrointestinal AEIs, OR 0.28 (95%CI 0.04-0.93, p=0.08), but more musculoskeletal AEIs, OR 1.97 (95%CI 1.26-3.04, p<0.001), and more local reactions reported, OR 6.64 (95%CI 1.75-31.46, p=0.01). However, the latter should be treated with caution because GSK vaccine was only in the enhanced passive (yellow card) arm and this AEI was reported more by the yellow card arm.

The comparison using multivariate logistic regression between GSK vs. non-GSK in the 14-day post vaccination window showed that the OR of reporting an AEI for GSK vaccinated people was 2.91 (95%CI 1.76-4.90; p<0.001) compared with non-GSK. Method of surveillance showed EHR data mining to have an OR of recording an AEI of 4.07 (95%CI 2.51-6.69; p<0.001). Male gender is associated with lower levels of AE recording; the OR is 0.68 (95%CI 0.55-0.83; p<0.001).

Multivariate logistic regression comparing vaccinated and non-vaccinated over the whole study period showed a similar pattern of comparison between vaccines. In addition, being in a CMO defined high risk group (mainly chronic conditions) was associated with presenting with an AEI/IDE. The OR of reporting an AEI among those vaccinated was 2.07 (95%CI 1.90-2.26; p<0.001) compared with non-vaccinated. People within a high risk group were more likely to present with an AEI/IDE 1.72 (95%CI 1.60-1.86; p<0.001). Method of surveillance showed EHR data mining to have an OR of recording an AEI/IDE of 1.54 (95%CI 1.38-173; p<0.001). Male gender is associated with lower levels of AE recording; the OR is 0.71 (95%CI 0.67-0.75; p<0.001). It is likely that practice factors and other impacts such as propensity to consult may account for why these factors impact on the OR of reporting AEIs/IDEs.

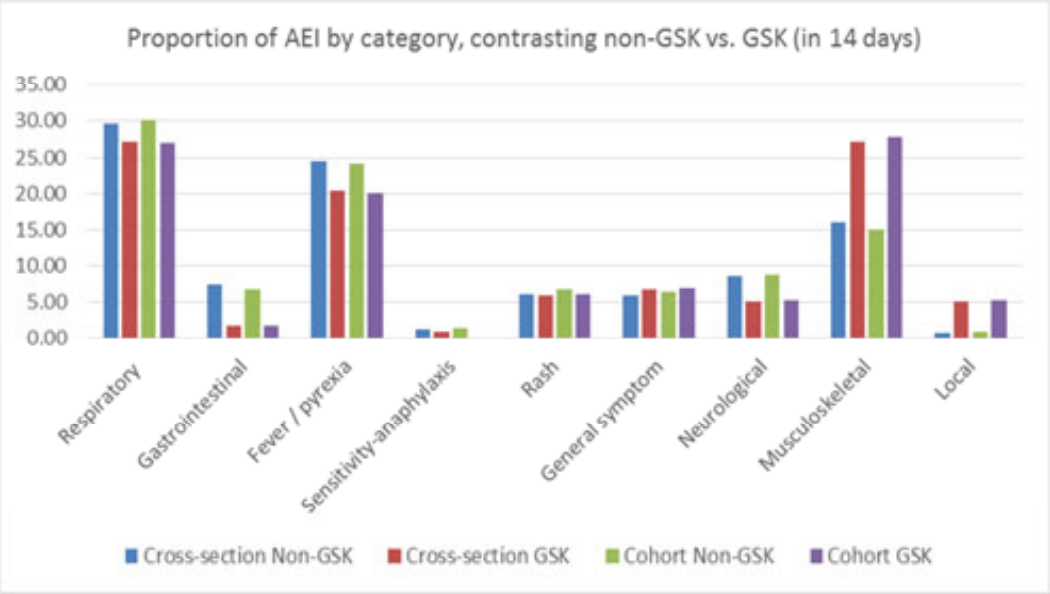
We propensity matched 8,006 patients (vaccinated with non-vaccinated) and found that those vaccinated had a greater OR of reporting AEIs/IDEs than those who had not been vaccinated OR 4.34 (95%CI 3.83-4.93). The only category where there was not a significant difference towards vaccinated people was “sensitivity or anaphylaxis”, OR 0.88 (95%CI 0.30-2.49).

2.4.4. Comparison of real-time with the cohort analysis

The cross-sectional population was larger and younger: the median age was 3 years younger (43 years vs. 46 years), and the mean age 1.6 years younger (43.0years (SD 23.54) vs. 44.6years (SD 23.30)). The proportion of young people, especially men aged 20-24years old, was higher in the cross-sectional analysis; the cross-sectional population has a greater proportion of people in the five most deprived deciles, and a lower proportion in four out of five of the least deprived deciles. The mean deprivation score was marginally lower (less deprived) in the cohort (13.5 (SD 8.95) vs. 13.3 (SD 9.97)). There was no difference in ethnicity between cross-sectional and cohort analyses, but there was slightly more ethnicity recording in the cross-sectional population (50.8% vs. 50.4%).

More people were vaccine-exposed in the cross-sectional study. 4.75% (n=163) and 7.28% (n=827) more people were vaccine exposed to the GSK and non-GSK vaccine on the repeated cross-sectional study; this represents an extra 1.4% of the population (n=990).

Figure 4 - Proportion of the different groups of EMA listed AEIs comparing Non-GSK with GSK for both the repeated cross-sectional and cohort studies for the 14 day post vaccine observation period



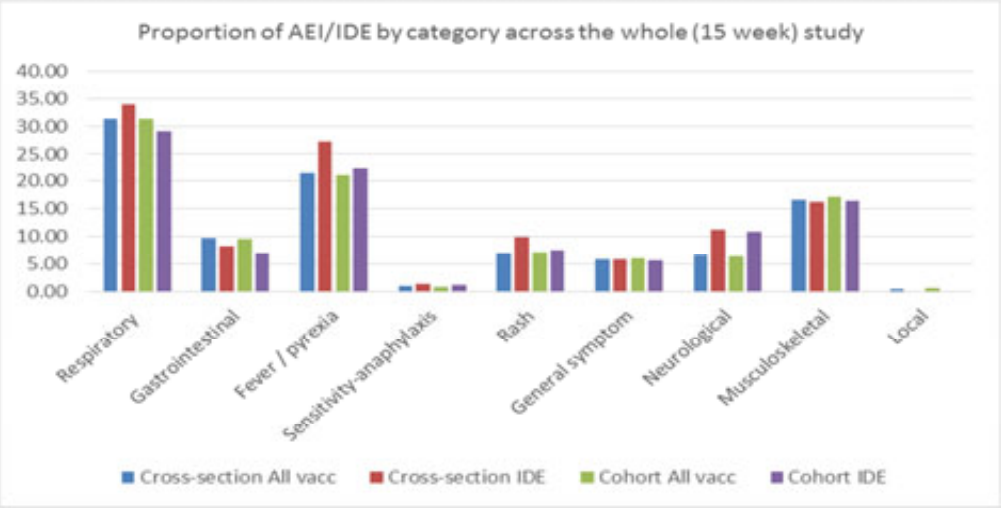
The repeated cross-sections identified more AEI/IDEs than the cohort analysis. The proportion with AEIs among vaccinated subjects in the 14-day window were 3.99% (95%CI 2.66%-5.32%, n=33) for non-GSK and 1.23% (95%CI 0.00%-3.07%, n=2) for GSK brand vaccine. (The proportion for GSK vaccines is actually lower but note the small numbers.) In a similar way there were higher proportions of AEI/IDE in the whole observation period in the repeated cross-sectional analyses.

One way that we observed differences in pattern of AEIs was by comparing the proportion of each class of AEI (Figure 4). In a study designed to detect differences such changes could lead to hypothesis formulation and further exploration.

Musculoskeletal and local reactions were a greater proportion of the AEIs reported for the GSK vaccine (though this difference related in this study to increased reporting of local effects via the yellow cards, as both GSK brand practices were in the enhanced passive surveillance arm). By way of contrast a greater proportion of gastrointestinal side effects are reported in the non-GSK vaccine.

The cohort analysis produced different rates and proportions of AEI/IDE from the repeated cross-sectional analysis. The rates and the proportions varied most between the two analyses when looking at background rates in the non-immunised (Figure 5).

Figure 5 - Proportion of the different groups of EMA listed AEIs/IDEs comparing Non-GSK with GSK for both the repeated cross-sectional and cohort studies; comparison for the 15 week study observation period



2.4.5. Feasibility analysis

The key results of our feasibility assessment were:

- The timeliness of vaccination data in the EHR was good. We separately extracted vaccine administration codes from prescriptions, and used the first date associated with this season's vaccine to ensure we recorded the correct date. However, delays in ethical approval and sign up meant reports did not start until week 42. There were problems in data flows from two practices. However, the data processes now set up could be instantly deployed in subsequent seasons.
- There was a high level of completeness of vaccination data in the EHR. The [redacted] rate of overall influenza vaccine uptake is 20.2%; the overall rate for these 9 practices is 20.7%. The remote data extract failed in some weeks, notably in the last weeks of collection from two sites (the two GSK vaccine sites). The [redacted] has a portfolio of around 130 practises from which data extracts are performed weekly; we have between 5% and 10% of practices fail data quality checks each week. However, the network has sufficient practices to cover this. We had a 22.2% (2/9) failure rate in the last week and instituted a local collection. The implication is that the cohort needs to have sufficient size to allow for a 5%-10% extract failure in any given week.
- The timeliness and completeness of AEI reporting in the EHR and through the yellow card reporting of AEI reporting in the EHR was good, but the response rate at 2% was low. Most AEIs were reported within a week, though a small number of cards were reported late. The non-GSK enhanced passive surveillance practice did not computerise all the yellow card AEIs.
- The accuracy of the data was good. Rates of the most frequently reported events are similar to the pattern reported across >1.3million patients in the [redacted] However, overall, a higher proportion of influenza vaccinated people in the [redacted] network presented with AEIs (14.1%, 95%CI 13.9%-14.2%), compared with the cohort in 2015 (11.9%, 95%CI 11.4%-12.4%). Similarly, there was a higher proportion of non-vaccinated patients in the [redacted] network presenting with AEIs (7.4%, 95%CI 7.3%-7.4%), compared with the cohort in 2015 (5.2%, 95%CI 5.0%-5.4%).

2.5. Discussion

2.5.1. The feasibility of setting up a near real-time AEI monitoring network

We demonstrated that it was feasible to recruit practices to participate in a brand-specific enhanced surveillance project. We applied the data extraction techniques developed for disease surveillance to EHR data mining to these volunteer practices. We extracted data that let us determine the characteristics of the population, vaccine exposure and AEI/IDE data. We had, however, to implement a local data collection to complete the data from two practices; a large pool of practices involved in this scheme would obviate this need.

Our sample was representative of age, sex and geography, but not for deprivation or ethnicity. The sample for future studies could have improved representativeness by recruiting more inner city practices. The rates of vaccine exposure were different between our enhanced passive surveillance practices and those involved in EHR data mining. We could change this in a future enhanced surveillance network.

A near real time enhanced brand-specific surveillance network could produce weekly or twice weekly reports of AEIs. The rates of AEIs could be compared between brands and with the background rates of the same conditions (we term them IDEs) in the non-vaccinated population, on a weekly basis. Enhanced passive surveillance (patients using the yellow cards) increased reporting of some elements (notably reporting of local reactions). Timely, complete data was extracted; comparison with the [redacted] surveillance system data suggests that vaccine and AEI/IDE data are complete.

Whilst we showed no major differences in rates between our enhanced surveillance brand (GSK vaccine) and other vaccines in overall rates of AEIs, we did demonstrate we could identify how all types of AEI/IDE were being recorded in primary care. The study was not designed or powered to show differences between brands, but we have demonstrated feasibility.

We have demonstrated the feasibility of providing timely data – we can process and present the previous week's data reported within four working days of the end of the recording period. Completeness and accuracy of the vaccine exposure data and AEI/IDE data were similar to that reported in a gold-standard primary care sentinel network.

2.5.2. Benefits of EHR data mining and enhanced passive surveillance (yellow card)

- **Strengths of EHR data mining:** EHR data mining should be part of this programme, because it provides accurate data about the denominator and vaccine coverage. It also provides complete and timely reports of AEIs and also informs if the same signal is present in the non-vaccinated by monitoring IDEs (we use the term "signal" to mean any change in data that leads us to form a hypothesis about possible causal relationship with vaccine exposure). This is important if a signal present in both vaccinated and non-vaccinated is unlikely to have a vaccine-related aetiology. The EHR data mining process supports both the repeated cross-sectional study, and also allows longer-term follow up of AEIs (rather than just the first week) and with its more stable denominator should give reliable rates.

  Patients attending hospital were identified from primary care data, and whilst this data may not be complete there is no reason to suppose there would be bias in recording within

practices between vaccinated and non-vaccinated patients. This part of the surveillance system can provide a measure of the number of more severe AEIs. Presentation of rates of admission associated with these AEIs in non-vaccinated subjects is reassuring and helps their interpretation.

  - **Near real time repeated cross-sectional analysis:** This should be able to rapidly produce a signal if one is present in the surveillance data.
  - **Retrospective cohort analysis:** Enables precise rates to be calculated. Captures rates of AEI/IDE in the cohort. Enables longer term follow up of any sequelae/severe AEIs.

- **Strengths of the enhanced passive surveillance "yellow card" scheme.** The strengths of the yellow card system is that it can be given to everyone presenting for influenza vaccination. It could be promoted to groups of patients underrepresented in routine data (e.g. men). Its other advantage is that it appears to improve reporting of some AEIs, notably local reactions to the vaccine.

2.5.3. Limitations of the EHR data mining and enhanced passive surveillance "yellow card" scheme

- **Limitations of the EHR data mining.** The limitations of the EHR data mining process is that data are largely derived from those who consult, some groups are underrepresented (e.g. men) and patients may not take the time and trouble to come in and report any influenza vaccine problems.

  Our EHR data mining findings may have been dominated by patients with a propensity to consult. This is a likely confounding factor. We know men consult less than women and consistently across all of our logistic regression models male gender was associated with lower reporting of AEI and IDEs. People with chronic disease also reported more AEI/IDEs and this may also have been related to propensity to consult. Future enhanced passive surveillance may need to be designed to be more inclusive of less represented groups.

  We note that the rates of AEI and IDE were higher in our EHR data mining arm. This may have reflected practice characteristics and/or that these practices' attention was on how they would distribute and collect data via the yellow card scheme. Our practice liaison officer's impression is that whilst the EHR data mining practices' attention was on the recommended code list, those of our enhanced passive data collection practices was on this novel use of the yellow cards.

  - **Near real time repeated cross-sectional analysis:** These analyses capture more patients. Near real time repeated cross-sectional analysis should be able to rapidly identify possible signals, should one or more be present in the surveillance data. However, they may miss vaccine exposure in patients who join the practice and underestimate AEIs and IDEs in people who leave. The population that moves in and out of the practices are younger and less likely to be in a high risk group. Additionally, problems often precipitate registration with a practice, so higher rates of presentation in the repeated cross-sectional analysis group may reflect this.
  - **Retrospective cohort analysis:** Whilst this type of analysis enables precise rates to be calculated by capturing rates of AEI/IDE in the cohort and enables longer term follow up of any sequelae and severe AEIs, it is inevitably retrospective and not

going to produce real time signals as is required. It does not meet the needs for detecting signal in real time during vaccination.

- **Limitations of enhanced passive surveillance "yellow card" scheme.** Whilst this card added to reporting, the principal problem was its low response rate. Only 2% of yellow cards were handed back. If they ran separately from the EHR data mining they risk giving sporadic data that is hard to interpret.

2.5.4. Recommendations for real-time monitoring:

Our recommendation is that the EMA should implement real-time monitoring based on a combination of the strengths of the different elements of this research:

- **EHR data mining.** EHR data mining should provide information about practice characteristics and the denominator, vaccine exposure and AEIs.
    - **Repeated cross-sectional data extraction.** Data extraction should be carried out weekly (or twice-weekly) to look for a signal. Case-matched controls or the use of control charts may provide better ways of detecting whether a signal seen in AEIs is likely to have a vaccine-based aetiology. The group of participating practices should be of sufficient size that failure of 5% per week should still provide sufficient sample. We have demonstrated that we can adapt [redacted] technology to do this.
    - **Enhanced statistical analysis of repeated cross-sectional data extraction.** Additional statistical techniques such as statistical process control or use of control charts might enhance the ability of the surveillance/repeated cross-sectional data to detect signal. Such techniques may be facilitated by a longer run-in of data collection through to the start of immunisation and the availability of multiple years' data.
    - **Cohort analysis**. Calculations of benefit-risk require accurate rates of disease. More severe possible AEIs need very careful follow-up. A mid- and end of season cohort analysis could provide definitive rates and reveal details of possible associations. It will also capture events that take longer to develop or have longer more severe impact.
- **Enhanced passive surveillance "yellow card" scheme.** This adds value, but if used alone the response rate is too low (2%) to be useful. This enhancement produced more reports of local reactions. It is also a potential method that can be built up and targeted at groups who present less (e.g. men).

Our recommendation is that EMA should establish a network of people involved in EHR data mining in real time, with strict data quality requirements. The principal surveillance method should be weekly repeated cross-sections. However this should be augmented by a "yellow card scheme" with definitive rates of AEI and longer term follow up of possible AEIs being added to by an end of season cohort analysis.

2.6. Conclusion

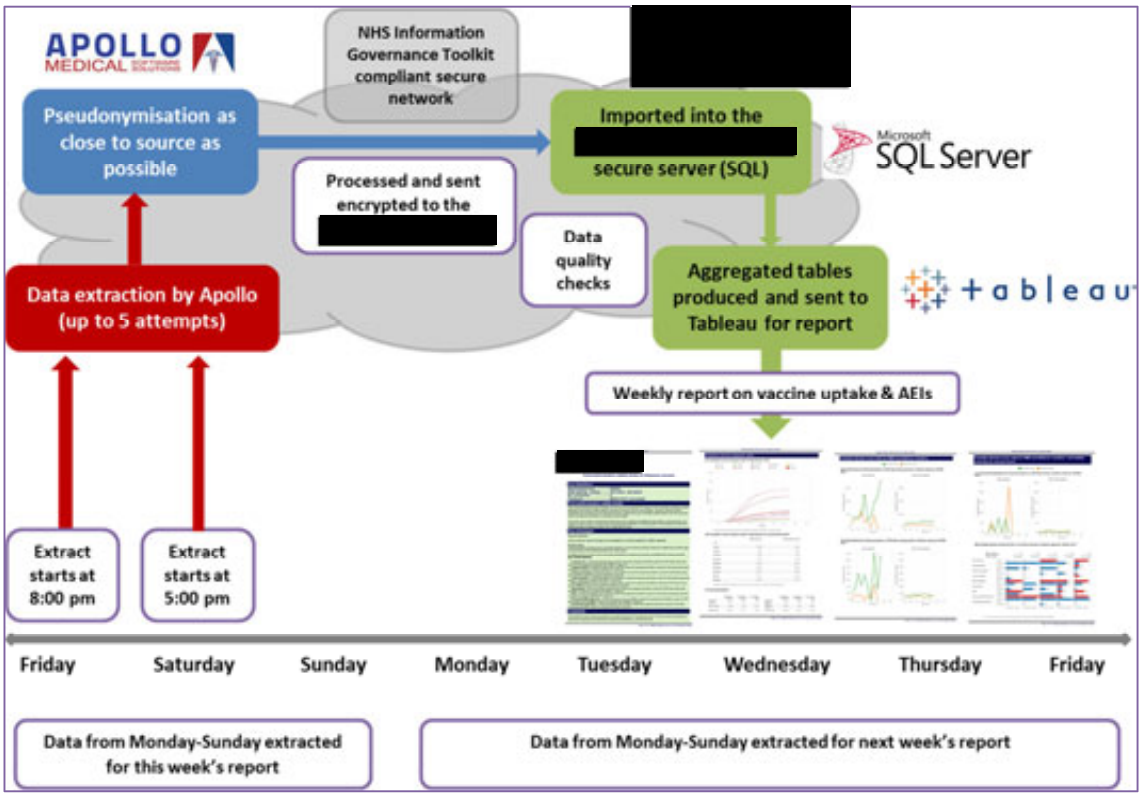
The study demonstrated the feasibility of setting up a network that could rapidly detect the signal originating from a significant change in AEIs associated with influenza vaccination. We recommend a process comprising a hybrid EHR data mining approach enhanced by a targeted yellow card scheme.

3. Introduction and background

In response to a recent expansion of national vaccination programmes across Europe, the European Medicines Agency (EMA) has released interim guidance on enhanced safety surveillance for seasonal influenza vaccines[1]; this sets out new standards for surveillance. The aim of the EMA enhanced safety surveillance is to rapidly detect a significant increase in the frequency or severity of adverse events of interest (AEIs), which can be local, systemic, or allergic reactions, indicating a potential or more serious risk, as the exposure to the vaccine increases in the population.

The guidance describes three types of enhanced surveillance: Active (post authorisation surveillance); enhanced passive surveillance; and electronic health record (EHR) data mining. This report outlines the results of a feasibility study run in collaboration between GlaxoSmithKline (GSK) Vaccines and the [redacted] Active or post authorisation surveillance is beyond the scope of this study. Our focus was on testing the feasibility of using enhanced passive surveillance and EHR data mining to rapidly detect signals, should unexpected AEIs occur.

Figure 6 - Overview of the weekly data extraction process developed at [redacted] for the [redacted] (implemented March 2015) and adapted to provide weekly AEI reports



The [redacted] within the [redacted] at the [redacted] is highly experienced at working with routine health data. Pertinent to this study, the group has led the design and implementation of the data and analysis hub for the [redacted] which was operationalised in March 2015 (Figure 6). [1]

The research group designed and built a data processing system, with the design benefiting from over 15 years of work processing routine data for observational[2] [3] [4] as well as interventional studies[5] [6]. The methods developed by the [redacted] in providing data and analytics to the [redacted] for influenza surveillance were applied to this in-depth surveillance system, with a focus on vaccine safety. The data processing, analytics capability, and leadership of the [redacted] ([redacted] is [redacted] is based at the [redacted]

Table 1 - Overview of the [redacted]

[redacted]	
What is the [redacted]	The [redacted] is the gold standard sentinel network[7] in primary care surveillance.
What is the coverage of the network?	The [redacted] network of practices gives national coverage of 1.5% of the population.
How often are data uploaded?	Data are uploaded from the network weekly to a secure sever, with the option to switch to twice weekly uploads at time of epidemics.
Are data reliably uploaded each week?	The data extract is from a steadily increasing pool of 130 nationally representative practices. Around 120 practices upload in a timely way and are usable each week. Quarterly bulk extracts ensure continuity of data for major reports.
What is the main focus of the network?	The [redacted] work mainly comprises surveillance sponsored by Public Health England (PHE) and is PHE's main source of primary care surveillance data, particularly for influenza.

Routine data collected in English primary healthcare have been widely used in research[8], and they have known strengths and limitations[9]. UK general practice has a registration-based list system, which has been highly computerised since 2004 with consultation records created by family doctors in real time during the clinical consultation. In the current study, data routinely collected as part of clinical consultations in primary care were extracted from nine general practitioner (GP) practices in order to estimate medically attended AEIs.

Patients who were exposed to the seasonal influenza vaccine had their vaccination date recorded. AEIs recorded 14 days following vaccination, and during the entire study period, were extracted from the routinely recorded clinical data. Three of the nine GP practices additionally gave an AEI reporting card (Yellow Card scheme operated by the Medicines and Healthcare Products Regulatory Agency, MHRA) to every patient who was vaccinated, asking them to report any AEIs on the card and return to the practice, for up to 14 days after their vaccination.

The vaccinated population included registered patients who received the seasonal influenza vaccine over a period between 24/08/2015 (week 35) and 06/12/2015 (week 49). This pilot

[1] *Submitted for publication: Correa A, Hinton A, McGovern A. et al., Cohort profile: Royal College of General Practitioners Research (RCGP) and Surveillance Centre (RSC) sentinel network. BMJOpen 11/1/2016*

set out to provide safety estimates early in the immunisation season, as the aim is to identify any potential AEIs before a large proportion of the population has been vaccinated with the vaccine, according to the EMA guidance. This study aimed to detect and evaluate increases in reactogenicity using two analysis methods:

- Weekly repeated cross-sectional surveillance reports (delivered in near real-time) of the incidence of AEIs in the vaccinated subjects. Because of the lack of historical background rates of AEIs in the same population, we used the incidence of the same conditions in the non-vaccinated population in the same practices as a comparison[2]. We refer to these same conditions when found in the non-vaccinated as illness-disorder episodes (IDEs). These studies provide valuable information about who is getting AEI/IDEs, where and when in time.

- Retrospective cohort study at the end of the study period to assess in depth statistical differences in the reported rates between the vaccinated and non-vaccinated populations. Cohort studies have the advantage of allowing the direct measurement of incidence in exposed and unexposed groups. They allow examination of multiple effects on an individual exposure and can explore the temporal relationship between exposure and disease.

For both methods, we also made a comparison between the GSK brand of influenza vaccine (identified by batch number or specific prescription) and other brands of influenza vaccines administered. Data quality is vital for any study based on routine data; and the key feasibility indicators we use in this study relate to data quality. The [redacted] research group has been at the forefront of developing methods of defining and measuring data quality[10]:

- Most definitions of data quality focus on the completeness and accuracy of the data[11].
- Currency[12], positive predictive value, and sensitivity[13] all add dimensions of data quality.
- Additional features relate to the provenance, lineage, and traceability[14]. However, these are less relevant to our study where we are looking at recently recorded data, namely vaccination data, and data about AEIs and IDEs.
- The most recent definitions focus on functionality, i.e. are data fit for purpose[15].

The completeness, accuracy, and timeliness of the data are the key elements in assessing its fitness for purpose in the context of this study.

The rationale for this study was to explore whether enhanced, "real-time" surveillance is practicable and feasible within a clinical settings and possible every year. The pilot set out to demonstrate the capability of routine data to be part of pharmacovigilance systems for influenza vaccines, being able to rapidly detect and evaluate potential new safety concerns early on in the influenza season before highest vaccine coverage is achieved.

[2] Herein, the conditions of interest outlined in the EMA guidance will be referred to as adverse events of interest (AEI) in the vaccinated population, and illness/disorder episode (IDE) in the non-vaccinated population.

4. Objectives

The study objectives, as set out in the protocol, were:

Primary objectives:

- Weekly estimation of vaccine coverage, by age strata,(risk group), and by vaccine brand
- Weekly reporting of AEI rates among subjects vaccinated against seasonal influenza, by age, (co-morbidity) from the GP practices using the EHR-data mining method, and those using the card-based surveillance system.

These objectives describe the key data required from the study (1) data about vaccine coverage and (2) data about AEIs. We planned a weekly cross-sectional surveillance report to provide this information. We subsequently carried out a retrospective cohort study to provide confirmed rates.

Secondary objectives:

- To assess the completeness of the vaccination data in the EHR-data mining and card-based surveillance systems
- To assess the timeliness of vaccination data in both surveillance systems (we used EHR-data mining and card-based surveillance systems)
- To assess the completeness of AEI reporting in both surveillance systems
- To assess the timeliness of AEI reporting in both surveillance systems
- To assess whether the rates of the most frequently reported events are compatible with expectations from published rates in a comparable population.

This secondary objectives relate to the assessment of the evaluation of and quality assurance of the process.

5. Methods and population

5.1. Overview

This study utilised two different surveillance approaches and two methodological approaches for the analysis of data:

1. Surveillance methods:

a. EHR data mining: When we refer to the EHR data mining group in the report we are referring to the practices (n=6) who *only* had data mining. Whilst all (n=9) practices we recruited had their routine clinical data automatically extracted on a weekly basis (i.e. had EHR data mining); three in addition took part in enhanced passive surveillance, described in more detail below. All practices were advised to record data into each patient's EHR in the usual way, with an emphasis on using the preferred codes list presented to the practice by the research team (listed in Table 3). Practitioners were also given a prompt list to go on the side of their computer screen.

b. Enhanced passive surveillance: Three out of the nine practices also distributed a reporting card, the yellow card, to patients receiving the seasonal influenza vaccine. Patients were asked to return the card to the practice within 14 days, and the results were then recorded by practice staff into the EHR. Data were then automatically extracted for all patients, as described in the EHR data mining surveillance method. Enhanced passive surveillance was therefore yellow card scheme plus EHR data mining (Figure 8).

2. Analysis methods:

a. Repeated cross-sectional reports: We created weekly surveillance reports, based on weekly cross-sectional data extracted from each practice, on the incidence of AEIs in influenza-vaccinated patients, the rates of the same conditions (IDEs) in non-vaccinated patients, and cumulative vaccination rates. These repeated cross-sections provided data in the week following its recording.

Inclusion & exclusion criteria of subjects: We included all patients registered on the day at the end of the week where a successful data extraction took place. We excluded non-NHS registered patients and those without a valid NHS number or date of birth. (Table 2)

b. Retrospective cohort study: We conducted a retrospective cohort study using the data collected between weeks 35 and 49 in 2015. We considered the cohort of people registered with the pilot practices through the whole observation period. Differences in the reported rates of AEIs for vaccinated patients and IDEs for non-vaccinated patients were evaluated using statistical methods.

Inclusion & exclusion criteria of subjects: Patents had to be registered for the whole period of observation (weeks 35 to 49) and also registered for one year prior to the start of the study to ensure we had reliable data about any long term condition that might affect their priority for influenza vaccination. Exclusion criteria were as for the repeated cross-sectional data extractions (Table 2).

Both methods compared the incidence of AEIs in the vaccinated and IDE in the non-vaccinated population, as many of these conditions have non-influenza vaccine related aetiologies. Additionally, we compared the rates of AEIs in the study sponsor's brand (GSK) with other brands. Finally, this study aimed to establish feasibility indicators. We provide an analysis of the feasibility of conducting this study on an ongoing basis. We focused on established dimensions of data quality: timeliness, completeness, and accuracy.

Table 2 - Inclusion/Exclusion criteria

	Inclusion	Exclusion
Repeated cross-section	Patients registered at the end of each week on which a report was constructed	Patients without a valid NHS number, recorded sex, or date of birth
Retrospective cohort	Patients registered at the beginning and at the end of the study period (week 35 to week 49), and with complete data going back one year to ensure CMO high risk condition was identified	Patients without a valid NHS number, recorded sex, or date of birth

5.2. Practice recruitment

Nine volunteer general practices were identified in England. All nine practices followed an EHR data mining method, with routine clinical data extracted for analysis, in order to identify possible AEIs. In three of the nine practices, an additional enhanced passive surveillance method was conducted. Patients vaccinated against seasonal influenza were given an AEI reporting card (MHRA Yellow Card, Figure) and asked to return it to the practice within 14 days post-vaccination; the data of any returned cards were then recorded into the practice's EHR system, and clinical pseudonymised data subsequently extracted.

Figure 7 - Yellow card provided to patients to report any AEIs

Recruitment efforts were focused on ensuring adequate representation of influenza vaccine brands (GSK and non-GSK), geographical location (North and South; and urban and rural), EHR system (Egton Medical Information Systems (EMIS) – EMIS Web; The Phoenix Partnership (TPP) – TPP SystmOne; and In Practice Systems (INPS) – Vision), and type of surveillance method being undertaken (enhanced passive or EHR data mining). The final selection of volunteer practices is set out in Table 3.

Table 3 - Characteristics of pilot practices

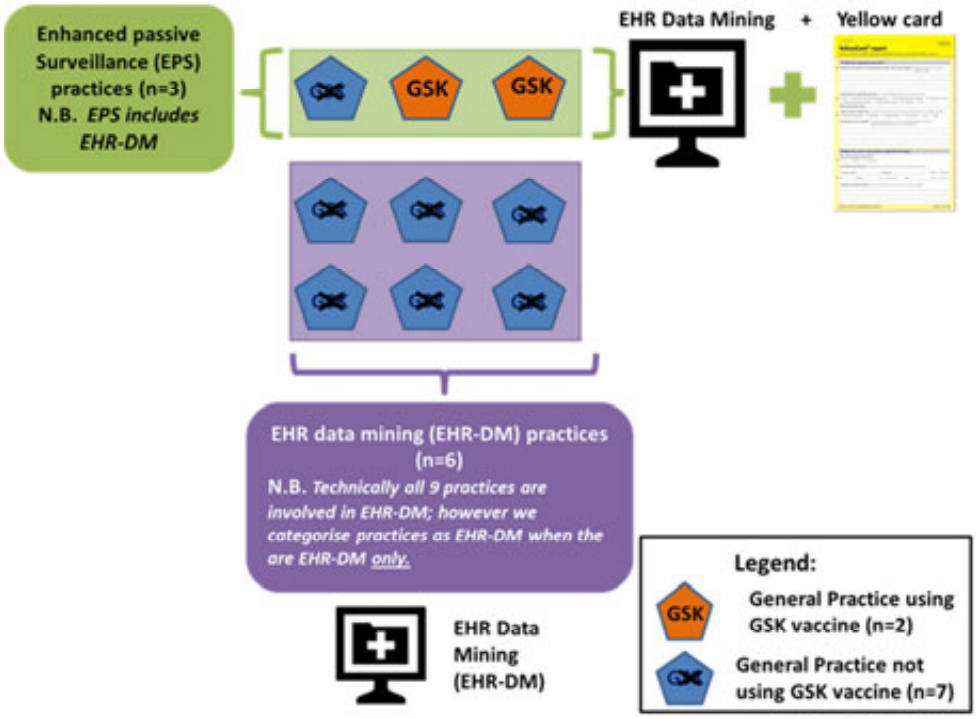
Participation	Clinical System	Registered population	Clinical Commissioning Group (CCG)	Location (North/South)	Location (Urban/Rural)	GSK Vaccine
Enhanced passive surveillance	TPP SystmOne	13,488	NHS Mid Essex	South	Urban	No
Enhanced passive surveillance	EMIS Web	9,925	NHS Warwickshire North	North	Urban	Yes
Enhanced passive surveillance	EMIS Web	8,768	NHS Cumbria	North	Rural	Yes
EHR data mining	EMIS Web	7,036	NHS Leeds West	North	Urban	No
EHR data mining	TPP SystmOne	9,153	NHS Ipswich and East Suffolk	South	Rural	No
EHR data mining	EMIS Web	2,384	NHS South Tyneside	North	Rural	No
EHR data mining	EMIS Web	11,456	NHS Guildford and Waverley	South	Urban	No
EHR data mining	EMIS Web	11,577	NHS Cambridgeshire and Peterborough	South	Rural	No
EHR data mining	EMIS Web	9,287	NHS Cambridgeshire and Peterborough	South	Rural	No

We directly approached 257 practices and invited them to participate in the study. Of these, 204 were reported to be using the GSK seasonal influenza vaccine during this season, whereas the remaining 53 practices used vaccines from a variety of brands. Interested practices were asked to confirm, at the point of recruitment, the vaccine brand they were to use that season. General practices are generally independent professional partnerships and make their own decision about which brand of influenza vaccine to purchase. Generally, they purchase a single vaccine for the practice prior to the start of the influenza season.

English general practices have a registration-based list system, where patients register with a single GP who provides primary health care; this includes immunisation against seasonal influenza and other diseases. The individual practice, typically with about 8,000 registered patients, selects which vaccine to purchase year by year.

- Two of the 204 practices using GSK vaccine expressed interest to participate and were included in the study; both of the GSK practices that were recruited used the quadrivalent influenza vaccine during their vaccination season. The two GSK practices only agreed to join as part of the enhanced passive surveillance, so there were no GSK practices in the EHR data mining surveillance arm.
- Fourteen of the non-GSK practices expressed interest in joining, and seven of them were selected to participate.
- The final study comprised nine practices of which three tested the feasibility of enhanced surveillance (two of these used GSK brand flu vaccine) and six (all non-GSK brand) who participated in EHR data mining (Figure 7).

Figure 7 – Diagrammatic representation of the practices who took part in the study.



There were nine practices recruited to this study. Two practices used GSK brand influenza vaccine (orange), and seven practices were not GSK brand (blue). All practices had their EHR mined weekly to extract data, but three practices additionally collected data via yellow cards, which they then recorded into the patients' EHR

- Three practices had EHR data mining plus gave those vaccinated a Yellow card. We term this the **enhanced passive surveillance** arm.
- Six practices had EHR data mining only. We describe these as the **EHR data mining** arm.

The two practices using GSK brand vaccine were both in the enhanced passive surveillance arm. The analysis in this report and in the weekly reports is disaggregated by surveillance method (enhanced passive or EHR data mining) in the manner outlined above.

At the point of recruitment, practices were asked to provide various details about the characteristics of their practice population, in order to determine whether they were suitable for the study. The registered population are outlined in Table 3 - Characteristics of pilot practices, as reported by the practices, but it does not represent the same number of patients used for either of the two analyses from that practice. For the weekly reports, we considered patients with a valid NHS number and a complete date of birth, and who were registered for the entirety of the analysis week. For the cohort analysis, we considered patients with a valid NHS number

and date of birth, and who were registered throughout the study period (weeks 35-49 in 2015) and who had at least one year of complete data prior to that date.

Figure 8 - Geographical distribution of pilot practices

A formal service level agreement (SLA) was established with the volunteer practices, consenting to the use of their routinely collected data for this vaccine safety surveillance study. Two of the practices were selected within the same clinical commissioning group (CCG) area, as can be seen in Table 3 - Characteristics of pilot practices. A CCG is the local NHS body that commissions health services for its local population. The geographical distribution of the practices was as broad as possible to ensure representativeness; Figure 8 outlines the location of each practice within England.

5.3. Data extraction

The method of data extraction and governance procedure has been developed by the [redacted] in partnership with [redacted] and PHE, using an approved provider, Apollo Medical Software Solutions Ltd. This provider extracts data using the Apollo automated extraction system. Communication is via a SOAP (Simple Object Access Protocol) web service, where no special firewall configuration is needed. In our study, data extracts took place on a weekly basis. However, we are able to extract data twice per week and could increase the frequency of the reports, if concerns were raised. This data could be used to identify a signal[3] [16] in a pre-specified monitored AEI/IDE; this method could also be used to test out a new hypothesis or interaction.

There is a back-up system for extraction, should the Apollo system fail; this is an NHS-approved data extraction tool called MorbIdity QUery information Export SynTax (MIQUEST). We have over 15 years' experience of using this tool in a number of disease areas[17,18], including providing

[3] We define signal as: *A suspected causal association sufficient for hypothesis formulation*

MIQUEST queries for a national audit[19], and linking MIQUEST-extracted data to other datasets[20]. For two of the pilot practices, Apollo was unable to successfully extract the complete dataset in the last two weeks of the study, so the team visited these practices to extract the relevant data directly using MIQUEST.

Data extractions were conducted in accordance with the [redacted] standard operating procedures in data extraction, pseudonymisation, and transfer. All data processing and analysis was conducted within the secure IT environment of the Research Group at the [redacted] The information security policies and procedures of the research group have been approved by the NHS Health and Social Care Information Centre (HSCIC). Details of the departmental information governance policies and procedures can be found in: http://www.clininf.eu/about/information-governance.html

We only extracted coded data (Read code version 2 and CTV3), i.e. where the GP or other health professional codes a disease, symptom, procedure, or investigation into the EHR[21]. This was only for patients without an opt-out code; this is a code that is recorded by a clinician whenever a patient opts out of allowing their practice to share their data. The prevalence of these is around 0.6%, in our experience – based on the difference between the non-opted out population and the stated list size. Also, people with long term conditions are less likely to opt-out. However, numbers up to 700,000 are quoted as having opted out[22]; based on an English population of 56 million, this would give an opt-out rate of 1.25%.

Coded data in the EHR in the English NHS have a set data format; there is a code for the clinical data items (e.g. disease, symptom, examination finding, investigation result, prescription, treatment, etc.), and also associated fields. These associated fields include the date when the episode occurred (we refer to this as the event date), the recording date of the event, numerical values (temperature, cholesterol levels, etc.), and other fields. Free text was not extracted due to the possibility of inclusion of patient identifiable information, and hence breach of a patient's common law right to privacy. The majority of the large volume of research that has come out of UK primary care is based on coded data[23].

The richness of primary care data allowed us to detect potential AEIs, and identify relevant risk group variables, vaccination status, and demographic characteristics of the patients. The study period went from week 35 2015 (beginning August 24th, 2015) to week 49 2015 (beginning November 30th, 2015 and ending on December 6th, 2015). We also extracted data from at least one year prior to the start of the study, in order to determine which people belonged in the Chief Medical Officer's high risk group categories for influenza vaccination[24].

At the point of data drop, the data were filtered and processed through a pseudonymisation package encrypting the NHS number. All data were strongly encrypted using a combination of symmetric and asymmetric encryption algorithms: triple data encryption standard (DES)[4] and

[4] This is often referred to as "Triple DES" or "3DES", which is the commonly used name for the triple data encryption algorithm (TDEA, also written Triple DEA) symmetric-key block cipher.

RSA 1024[5] before transmission, and utilised public and private key pairs unique to the project. The application of pseudonymisation at this stage also allows the same algorithm to be applied to additional data sources, which would allow linkage in future years to other datasets; for example, the linkage of patients' primary care and hospital data, without a need to identify a person.

Once extracted, the data is stored in a secured SQL database server at the [redacted] The data are managed and configured in SQL to produce aggregated tables, which are automatically linked to a Tableau business intelligence server, where reports can be generated each week. The setup of the aggregation scripts and the report formatting require a lead time of several weeks. Once setup, the report can be generated programmatically in less than an hour from the point of the data being imported into the SQL database server.

5.4. Ethical approvals

Ethical approval for this study was sought from the [redacted] via the Integrated Research Application System (IRAS). This is an integrated online system for all applications to regulatory bodies for conducting health research in the UK. As no major ethical issues were raised and patients were not receiving a new intervention, our application was deemed suitable for the [redacted] rather than a full ethical review. This is a committee within the REC structure which provides a two-week review for studies that do not raise major ethical issues. The approval was obtained on July 14th, 2015 (REF: 15/LO/1254).

As part of the ethical approval, we were required to provide the pilot practices with materials to inform the patients of the ongoing study at the surgery. These materials, which included posters in visible places, informed the patients of the study and stated the patients' right to opt out of having their data extracted. If a patient wished to not participate in this study, an opt-out code was included in their EHR. Moreover, the yellow card that was handed to patients in the enhanced passive arm of the study was accompanied by an information sheet, which stated that patients would be consenting to the use of their data by returning the yellow card. This consent could be reversed at any point, by informing their GP.

One of the conditions of the ethical approval was that the study team needed to obtain Research & Development (R&D) permission from the relevant localities involved. For studies that have registered in the National Institute for Health Research (NIHR) portfolio, this R&D approval is centralised; however, this study was not part of the portfolio, and approval was then sought locally. The relevant localities advised that, as the research management permission had already been provided by the recruited practices (in the form of an SLA), no further local approvals were needed. This is in line with guidance provided by the Department of Health in 2013[25], where independent contractors (such as GPs) were given the responsibility to decide whether to participate or not in research.

Finally, this report uses rates from the [redacted] network of practices to provide an assessment of the accuracy of the data. We followed the required process whereby we submitted a data

[5] RSA stands for Rivest, Shamir and Aldeman who founded RSA Laboratories. They created large numbers with only two prime factors, a core component of the encryption process.

request form alongside a copy of the final protocol and REC approval. The request was then considered at an [redacted] governance meeting for approval.

5.5. Exposure and adverse event measures

5.5.1. Exposure

It is current practice in the system that whenever a patient receives a vaccine in primary care, a prescription code of the vaccine should be issued specifying the brand and type of vaccine used, and a code for the vaccination administration "event" should also be recorded. Practices were advised to record both codes, to ensure data completeness. Whilst the overwhelming majority of influenza vaccination takes place in English general practices, some vaccines may be administered by pharmacists or as part of an occupational health scheme; these vaccines will only have an administration code, if the patient reports this to their GP.

We started exploring vaccinations from week 35 (beginning 24th August, 2015), but the majority of practices in the study began their large flu clinics on week 40. The national target timeframe for the influenza immunisation programme is from 1st September, 2015 to 31st January, 2016 in order to achieve maximum coverage and impact[26]. However, it is recommended that at-risk groups should be vaccinated as soon as the seasonal influenza vaccine becomes available, and to vaccinate before the influenza virus starts to circulate largely in the population (usually in December); the NHS recommends vaccination right through to March[27].

Patients were classified as vaccinated whenever either a prescription or administration code for an influenza vaccine were recorded in the patient's medical record. Whichever had the earliest date was taken as the vaccine administration date. Since a patient receives the influenza vaccine only once in the season, once a patient is considered to be vaccinated, they form part of the "vaccinated denominator" for the remainder of the study period. In other words, the "vaccinated denominator" is built cumulatively, with new vaccinated patients being added each week to the existing vaccinated patients.

This cumulative rate of vaccination, as a proportion of registered patients, is reported both in the repeated cross sections (up to the relevant week) and in the cohort analysis. Additionally, the cohort study reports a tabular summary of the population according to their vaccination status and brand, disaggregated by age group, surveillance method, risk group, and concomitant vaccines. The vaccinated denominator used in calculating the AEI rates was different for each type of analysis:

- **Repeated cross-sectional reports:** Since incidence of AEIs was reported on a weekly basis, the denominator for vaccinated patients was the number of patients registered that week who had received a seasonal influenza vaccine at most 14 days prior.

- **Retrospective cohort study:** We divided the cohort according to their vaccination status at the end of the study period (week 49), and we also noted the date. The denominator is the number of patients with a vaccinated status at the end of the study.

5.5.2. Adverse events of interest (AEI)

AEIs were the outcome measure of this study; we have included the rates for patients who had been exposed to the seasonal influenza vaccine and those who had not, where we refer to them as IDEs. The inclusion of IDEs is to aid interpretation of any apparent signal in AEIs. If both AEI and IDE codes show the same signal this is unlikely to be vaccine related. Data, such as hospital admissions, related to AEIs may be difficult to interpret without also having IDE data available.

Table 4 - List of EMA surveillance conditions and preferred codes given to practices

EMA surveillance condition	Read Code (5 Byte)	Read Code (CTV3)	Notes
Respiratory/Miscellaneous			
Conjunctivitis	F4C0.	XE16X	
Rhinorrhoea	1C83.	XM00h	
Nasal congestion	H1y1z	X77Gp	
Epistaxis	R047.	Xa96W	
Coryza	H00..	XE0Xl	
Cough	171..	XM0Ch	
Oropharyngeal pain	1922. 1CB3.	1922. 1CB3.	
Hoarseness	1CA2.	1CA2.	
Wheezing	1737.	XE0qs	
Gastrointestinal			
Decreased appetite	R0300	XM07Y	
Nausea	198..	X75qw	
Vomiting	199..	XE0rA	
Diarrhoea	19F..	19F2.	
Fever/Pyrexia			
Fever	165..	X76Dl	
Mild fever (<38.5° C rectal) Moderate fever (38.6-39.5°C) High fever (>39.5°C)	2E3..	2E3..	Please include level of temperature, to help us classify the fever
Sensitivity/Anaphylaxis			
Hypersensitivity reactions	SN52.	Xa5uf	
Anaphylactic reactions	SN501	X70vr	
Facial oedema	16J5.	Xa0ls	
Rash			
Rash	M130.	X50Ge	
Generalised rash	2I14.	XM07J	
General non-specific symptoms			
Irritability	225A.	225A.	
Drowsiness	1B67.	XM06R	
Fatigue	168..	1682.	
Neurological			
Peripheral tremor	1B22.	XE0rn	
Guillain-Barre Syndrome (GBS)	F3700	F3700	
Seizure/ Febrile convulsions	1B64. 1B6B.	XaDbE XM03l	
Headache	1B1G.	XM0CV	
Musculoskeletal			
Muscle aches/ myalgia	N2410	X75rs	
Arthropathy	N037.	X701f	
Local symptoms			
Local erythema	SP3y4 SP3y5 SP3y6 SP3y7	X75ty	

The AEI codes were determined using an iterative ontological approach[28,29] based on the EMA surveillance conditions of interest[30]. These conditions were aggregated under broad system categories to facilitate clinicians' awareness of the conditions and their reporting. The repeated

cross-section weekly reports, included in Appendix A, provide data about the AEIs based on the broad categories only. The retrospective cohort study reporting includes both the broad and specific categories. During the initiation visit, practices were given a list of preferred codes based on the EMA surveillance conditions; these are outlined in Table 4.

In addition, each practice was given ten (unless more were requested) laminated bookmarks with these codes for practice managers to attach to the side of each clinician's computer screen (where they record data into their EHR system), to prompt them and remind them which codes to use. All English primary care clinicians record data into their EHR system during or just after the clinical consultation[31]. For the purposes of analysis, the code list was expanded further to ensure that the data capture was as comprehensive as possible.

To maximise the data quality and capture of events, each of the practices was provided with a weekly feedback about the rate of AEIs recorded in their practice during the previous week (Appendix B). These weekly feedback reports began on week 42 (covering the period from week 40-42) and continued until the end of the study. In addition, the Practice Liaison Officer contacted practices regularly to ensure that GPs were using the suggested codes, and to establish whether clinicians had identified any additional adverse events that were not included in the original recommended list.

Similar to the vaccine exposure, the numerators for calculating the AEI rates were calculated differently for the two types of analysis methods:

- **Repeated cross-sectional reports:** A patient was counted in the numerator if they had an AEI code recorded in the EHR with an event date during the reporting week, and also a vaccination date occurring at most 14 days prior. We also counted non-vaccinated patients having an IDE, reflecting the same type of disorders as mentioned in the AEI list (but were not in any temporal relationship with influenza vaccination, because they did not receive the vaccine) for each reporting week to establish the background rate of these conditions. There was no attempt in the weekly reports to precisely match the period of time in which coding of an IDE might occur in a non-vaccinated patient, in the way that the vaccinated patients AEIs were considered only for a strict 14 days after vaccination.

- **Retrospective cohort study:** This report is set out differently from the weekly reports, as it is effectively a cohort study of patients registered throughout the study period. Within this report we make two sets of comparisons:
  - We consider patients who developed an AEI within a 14-day window following a seasonal influenza vaccination, as a proportion of all vaccinated patients. Within this group, we compare the GSK brand vaccine with the other brands of flu vaccine.
  - We also compare rates of AEIs/IDE in influenza vaccinated subjects compared with non-vaccinated subjects. We report rates of AEI/IDE occurring at any point in the whole observation period – i.e. from week 35 to week 49.

Our purpose was not to compare rates between vaccinated and non-vaccinated populations. Instead, it was to establish background rates so we could more reliably compare week-on-week rates. If a particular AEI gave a strong signal (i.e. rapidly increased in rate), it would be important to know if the same condition (labelled an IDE) gave the same signal in the non-vaccinated population. We made no attempt to match these two groups, as it is likely that the older and higher risk groups, who are recommended to receive the seasonal influenza vaccine, would have a higher propensity to consult the doctor; whilst the non-vaccinated population may be distributed differently and have a lower propensity to consult.

5.6. Statistical analysis

The statistical analysis and the disaggregated rates presented with 95% confidence intervals relate to the results from the cohort analysis.

5.6.1. Description of population

We provided a description of the study population, including key demographic characteristics such as age, gender, ethnicity, and deprivation scores (using the Index of Multiple Deprivation (IMD) based on each patient's Lower Super Output Area or geographical location[32 33]). For all of these, basic descriptive statistics were used such as mean, median, and standard deviation, where appropriate. We also conducted a comparison to national rates in order to provide an assessment of the representativeness of the sample of pilot practices for England

5.6.2. Disaggregated rates

We provide vaccination and granular AEI/IDE rates with 95% confidence intervals and with various levels of disaggregation for both the cohort and the cross section. Confidence intervals were calculated using the CRITBINOM[6] function in Microsoft Excel. This is a commonly used function that has been shown to produce exact confidence intervals for proportions[34]. Rates of vaccination (as a proportion of the registered population) were presented cumulatively over time, as a total, and disaggregated by age group, surveillance method used, vaccine brand, risk group, and concomitant vaccines (pneumococcal and shingles) administered.

AEI rates were reported as a specific surveillance condition/event (e.g. epistaxis, nausea, headache, etc.) and also as a higher level category (e.g. respiratory, gastrointestinal, neurological, etc.) for both the cohort and the cross section. Finally, we include a disaggregation by age group, risk group, vaccine brand, and type of surveillance only for the AEI rates in the cohort. AEIs and IDE rates were presented comparatively as two groups:

1. For vaccinated patients only: we compared rates of AEIs occurring 14 days post-vaccination between patients receiving the GSK vaccine and patients receiving a non-GSK vaccine.
2. For all patients in the cohort: we compared rates of AEIs/IDEs occurring at any point during the study period between patients who were vaccinated and patients who were not vaccinated.

5.6.3. Severity assessment

Additionally, to assess the severity of the AEI/IDE, we used the cohort data to explore whether concurrent hospitalisations happened as a result of the AEI/IDE, as well as recorded level of fever, if present. For the concurrent hospitalisations analysis, we considered all hospital

[6] CRITBINOM – this provides the inverse of the cumulative binomial (hence BINOM) distribution.

admissions recorded in primary care with an event date 10 days prior or post the AEI date. The reason for taking into account hospitalisations before the adverse event is due to the potential for time disparities between a patient reporting the AEI to their GP and a hospital report reaching the GP. For the fever, we provided a histogram showing the temperature distribution for all patients reported to have a fever; we also disaggregated this by the groups outlined above (AEI within 14 days post vaccination: GSK vaccine or non-GSK vaccine, AEI at any time: vaccinated or non-vaccinated).

5.6.4. Crude odds ratios

For the crude odds ratios, the logistic regression, and the propensity matching, we only used the cohort data. We calculated two simple odds ratios:

1. The probability of a subject developing an AEI 14 days post-vaccination, dependent on the vaccine brand used. Only the subset of vaccinated patients was used for this calculation.
2. The probability of a subject developing an AEI at any point during the study period, dependent on whether he/she had been vaccinated or not. All patients in the cohort were considered for this calculation.

We report the odds ratio for all AEIs/IDEs, and for each broad category of AEIs/IDEs.

5.6.5. Multivariate logistic regression

Additionally, we produced two multivariate logistic regression models using the same structure of the odds ratio (two different populations, explanatory and outcome variables), but expanding the explanatory variables to include age, gender, ethnicity, deprivation score, high risk group, method of surveillance, and concomitant vaccinations. It must be noted that the method of surveillance was determined at the patient level; only patients who were vaccinated in the practices within the enhanced passive arm were given a yellow card, while the non-vaccinated patients were not. Therefore, non-vaccinated patients in the enhanced passive arm are considered to be within an EHR data mining method of surveillance.

5.6.6. Propensity matching

In order to assess the odds ratio, we needed to ensure that the vaccinated and non-vaccinated populations were not fundamentally different. For this, we used a propensity matching method, as part of this report. It could be considered for matching subjects in the weekly reports in future. We only used the propensity matching method in the EHR data mining arm, as non-vaccinated patients were not classified in the enhanced passive arm, as outlined above.

The purpose of using this method is to reduce the reporting bias that vaccinated patients may have. Vaccinated patients may have a higher probability to report AEIs, due to being older or being in a high risk group. Matching them with a cohort of people who are equally likely to be vaccinated, but who did not actually receive the vaccine, reduces this bias. We developed a logistic regression model to determine the probability of getting vaccinated, using age, gender, ethnicity, deprivation score, and high risk group as explanatory variables; it must be noted that there may be other systematic bias between these groups, particularly propensity to consult, which can be explored in the future.

Using the fitted values from this model, we assigned each member of the EHR data mining cohort a probability of getting vaccinated, and we matched each vaccinated patient with a non-vaccinated patient with the same probability score (up to 2 significant figures). After conducting

the matching, our cohort was reduced to 8,006 patients; half of which were vaccinated and the other half were not, with each half having one counterpart with an identical vaccination probability. We then calculated the odds ratio of developing an AEI at any time during the study period for this matched cohort, dependent on vaccination status. We report all odds ratios with their respective confidence intervals. All of the logistic regression analyses were conducted using the statistical software R.

5.7. Measure of feasibility

We used established methods to ensure our data were collected in a way that were a) timely, b) complete, and c) accurate.

5.7.1. Timeliness

Our data are generally extracted twice weekly from practices, but analysed on a weekly basis. We can step up to twice weekly, if there are results of interest. We focus the timeliness report on the speed with which we report seasonal influenza vaccine and AEI/IDE data. We produced a first weekly report summarizing the data (vaccination and AEI/IDE data) within 8 weeks of vaccination starting in the study population.

However, a number of other factors impact on timeliness:

- University contractual timelines
- Ethical approvals
- Recruitment of practices
- Starting the observation period from the week that vaccines are available
- Collection of weekly practice surveillance data and feedback to practices about data quality
- Collection and analysis of data (vaccination and AEI/IDE data) from patients (or their carers) as part of the enhanced passive surveillance process, but also collection/extraction and analysis of data (vaccination and AEI/IDE data) in EHR data mining arm
- Understanding the lag between event data and recording data in NHS systems; definitive hospital data and diagnoses may not be available for days or weeks, and sometimes longer. (e.g. someone admitted to hospital with a rash may turn out to have meningitis, but this information may not be sent to the GP until after the patient is discharged).

5.7.2. Completeness and accuracy

The study needs an accurate and complete denominator. Computerised registration ensures this. Influenza vaccine data need to be complete, accurate, and brand specific. We can compare the rates with the vaccination monitoring taking place within the [redacted] We can also compare the rates of AEI/IDEs with the rates in historic [redacted] data. The [redacted] practices have been receiving feedback about data quality for some decades, resulting in the gold standard sentinel network, and being the main source of data for Public Health England's surveillance work[35] [36] [37] [38] [39]. The training put into practices in this study should achieve comparable data quality.

6. Description of the population

This section describes the population characteristics for both the cohort data and for the population included in repeated cross-sections (from week 35 to 49). Table 3 - Characteristics of pilot practicesprovides an overview of the registered population, as reported by the practices at the time of recruitment; this may vary as patients join or leave the practices. In the weekly reports included in Appendix A, the population was defined using repeated cross-sectional analysis; this means that the denominator in each report is equal to the number of registered patients for that specific week. If a patient leaves, they are not included in the subsequent report.

For the cohort, however, we extracted data for all patients in the study practices registered on the first day of week 35 (August 24th, 2015), who had not opted-out of data sharing, and with at least 1 year of complete primary care data up to this date. This historical data was needed to define each patient's risk group category. If a patient left after the cohort start date, they were still counted in the denominator; conversely, if a patient joined after this date, they were not counted in the denominator.

Table 5 - Cross section denominators (by method of surveillance and vaccine brand)

Real-time cross-sectional denominator		Method of surveillance		Vaccine Brand (vaccinated patients only)	
80635		Enhanced passive	EHR data mining	GSK	Non-GSK
Method of surveillance	Enhanced passive	N/A	N/A	3597	3607
	EHR data mining	N/A	N/A	0	8587
Vaccine Brand or vaccination status	GSK	3597	0	N/A	N/A
	Non-GSK	3607	8587	N/A	N/A
	Non-vaccinated	0	64844	N/A	N/A
Total		7204	73431	3597	12194

Table 6 - Cohort denominators (by method of surveillance and vaccine brand)

Cohort denominator		Method of surveillance		Vaccine Brand (vaccinated patients only)	
71407		Enhanced passive	EHR data mining	GSK	Non-GSK
Method of surveillance	Enhanced passive	N/A	N/A	3434	3342
	EHR data mining	N/A	N/A	0	8025
Vaccine Brand or vaccination status	GSK	3434	0	N/A	N/A
	Non-GSK	3342	8025	N/A	N/A
	Non-vaccinated	0	56606	N/A	N/A
Total		**6776**	**64631**	**3434**	**11367**

We used the week 49 denominator for the cross-sectional studies (N=80,635), with over 3,000 patients vaccinated with a GSK influenza vaccine and over 12,000 patients vaccinated with other brands of influenza vaccine. The denominator of the repeated cross sections varied each week. We recorded the smallest list of registered patients (79938 patients) in week 35, and the largest list (80977) in week 48 (Table 5). The cohort denominator was 71,407 people, with over 3,000 patients vaccinated using GSK brand influenza vaccine and over 11,000 vaccinated with other brands of influenza vaccine (Table 6).

Table 7 - Comparison of real-time with the cohort analysis denominator (by method of surveillance and vaccine brand)

Comparison of real-time with the cohort analysis denominator		Method of surveillance		Vaccine Brand (vaccinated patients only)	
		Enhanced passive	EHR data mining	GSK	Non-GSK
Method of surveillance	Enhanced passive	N/A	N/A	163	265
	EHR data mining	N/A	N/A	0	562
Vaccine Brand or vaccination status	GSK	163	0	N/A	N/A
	Non-GSK	265	562	N/A	N/A
	Non-vaccinated	0	8238	N/A	N/A
Total		428	8800	163	827

Figure 10 shows the age gender profile of the feasibility study practices standardised against the English census population, for both the cohort population and the cross-section. Women represent 49.8% of the cross-section, while men represent 50.2%; mean age was 43.01 (s.d. 23.5). Women represent 49.7% of the cohort, while men represent 50.3%; mean age was 44.61 years (s.d. 23.3). The comparison between the cross-section and the cohort shows that the cross-section population tends to be younger. This could be interpreted as the cross-section having a younger and more mobile population, who would be more likely to enter or leave a practice population.

The age-sex profile of the cohort study population showed that there is a slight underrepresentation of men aged 15-30, and children aged 0-4 against the national population. The cross-section study population appears more representative than that of the cohort, against a national population, but there is still an underrepresentation of children aged 0-4. Due to the method of extraction, where dates of birth are deleted, and an algorithm converts the month and year of birth into age, children under 1 year of age could not have been registered for the qualifying year. Figure 9 contrasts the cohort and repeated cross-sectional populations.

Figure 9 - Contrasting the size of the denominator for the repeated cross sections and the cohort

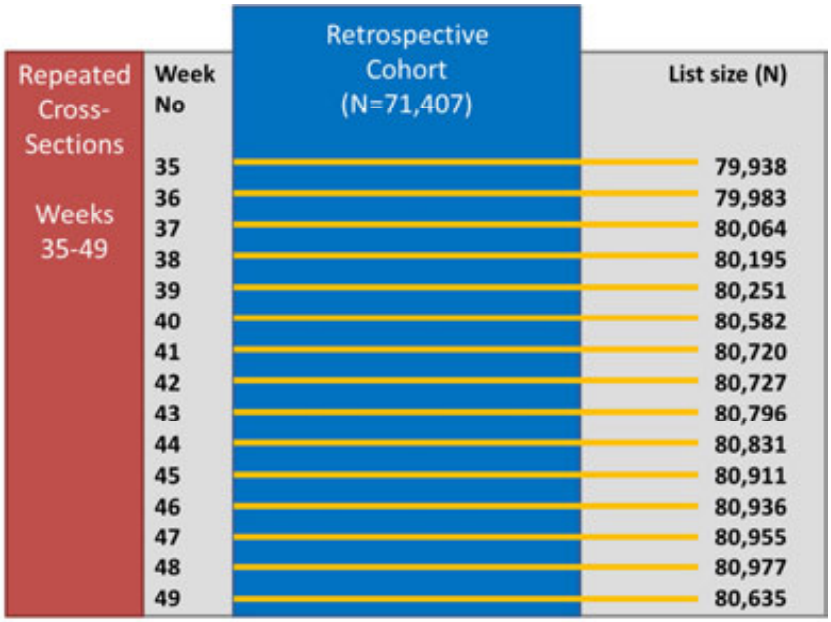
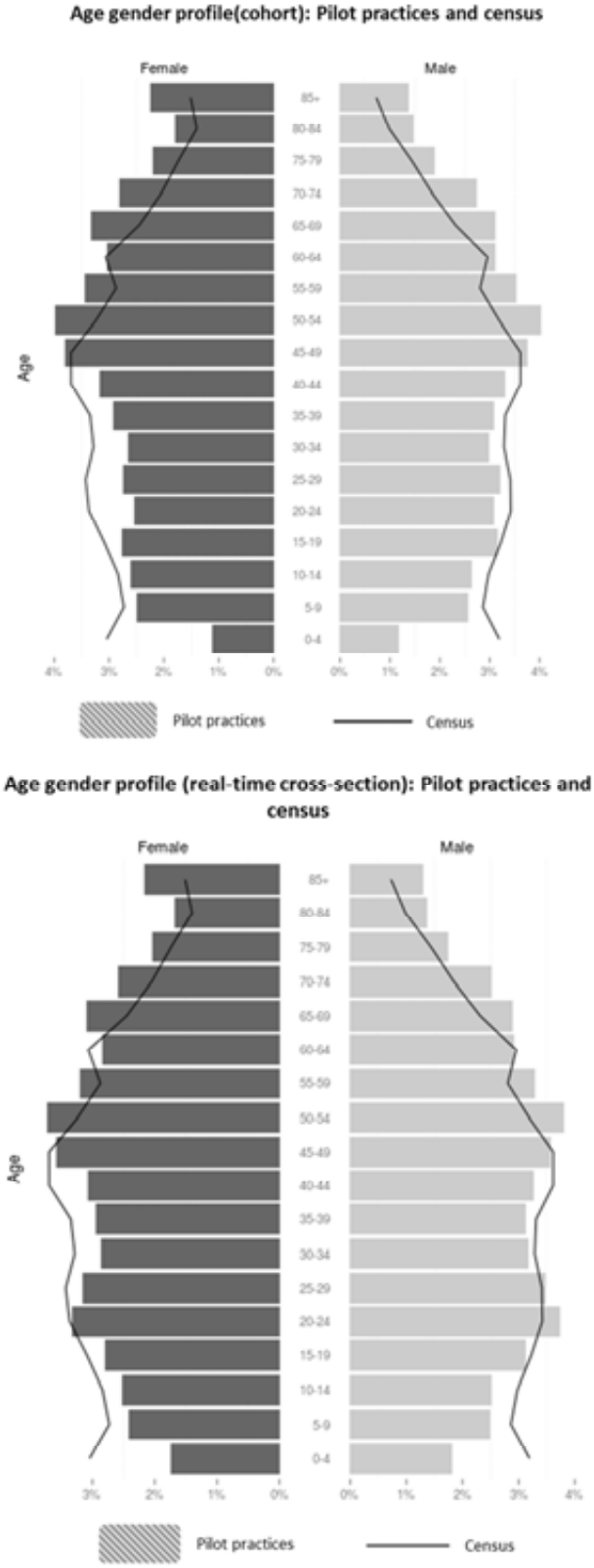
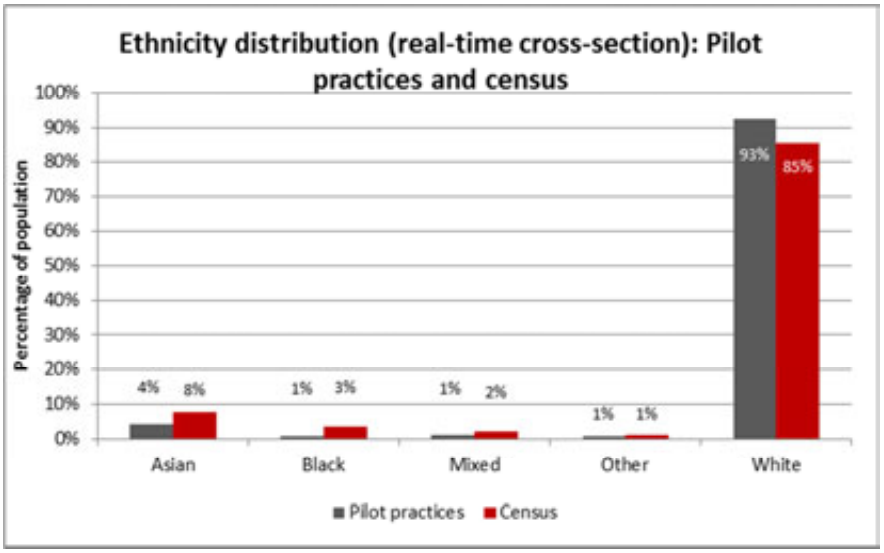


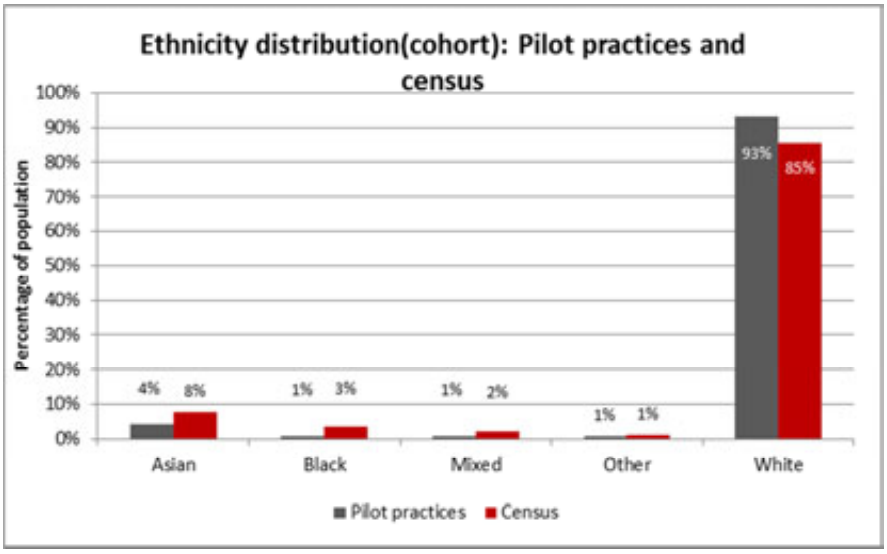
Figure 10 – Age-sex profile for both the cross section and the cohort: Pilot practices and census population



We identified an ethnicity category (based on the English Census 2011 categories) for 50.4% of the cohort and 50.8% of the cross-section. For those with a recorded ethnicity, the distribution is shown in Figure 11. Compared to the national population, both the cohort and the cross-section study populations have a higher proportion of people with a white ethnicity. This could be related to the lack of recruitment in London or in urban centres with a population higher than 1 million people. Comparing the cohort and cross-section, ethnicity distribution is not a population characteristic that is likely to change as patients enter or leave the pilot practices.

Figure 11 - Ethnicity distribution for both the cross section and the cohort: pilot practices and census





The mean IMD score for the cohort was 13.25 (s.d. 9.77) and 13.47 (s.d. 9.95) for the cross-section, compared to 21.8 for the national population. This implies that both the cohort and cross-section populations tended to be less deprived than the national average, as shown in Figure 12. Figure 13 shows the distribution of the IMD scores by deciles, where over 25% of the cohort and the cross-section was in the least deprived decile. Given the geographical

distribution of the pilot practices in rural or small urban areas, this could explain the over representation of less deprived people.

Figure 12 - IMD scores cumulative distribution for the cross-section and the cohort: pilot practices and census

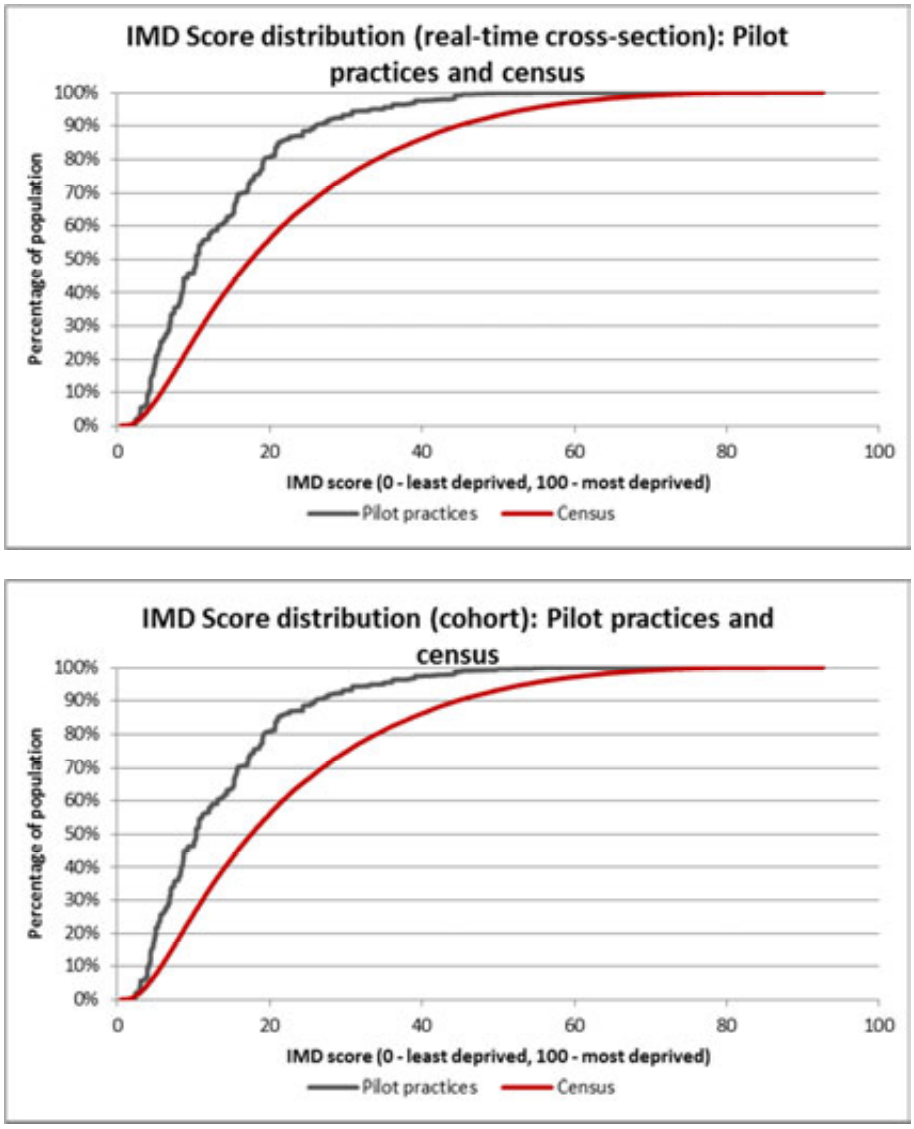
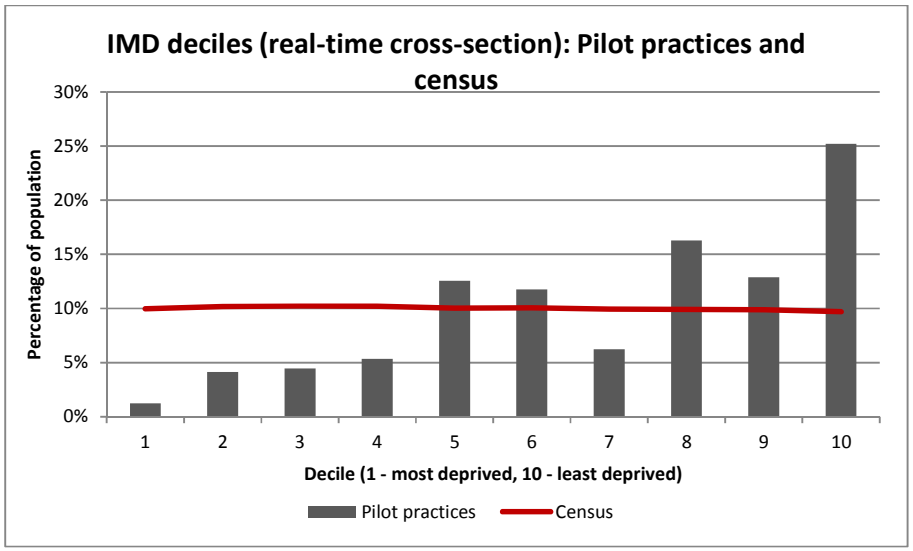
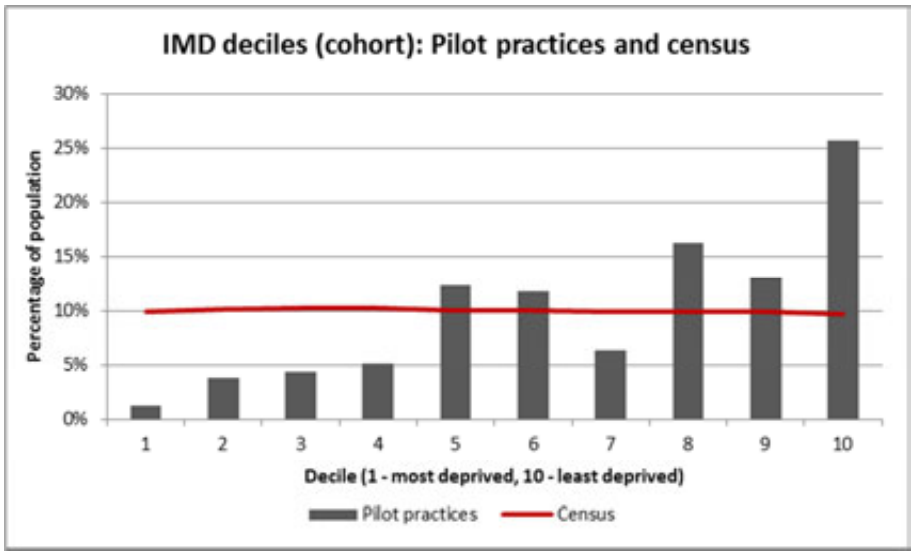


Figure 13 - IMD scores by deciles for the cross-section and the cohort: pilot practices and census





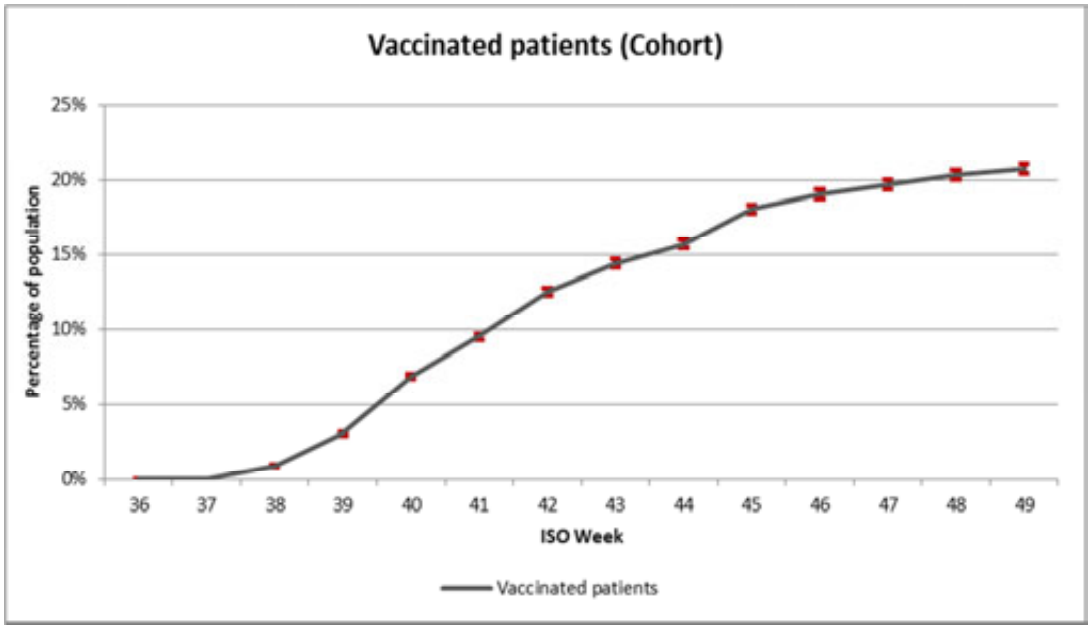
Due to lack of recruitment in large inner city areas, the population using the cohort and the cross-section methods of analysis was not fully representative of the national population. The age and gender profiles closely resembled that of England, but the ethnicity and socio-economic deprivation characteristics of the cohort were different. The cohort and cross-section populations were very similar, with the exception of age, where the cross-section population tended to be younger.

7. Exposure data

In this section, we show the rates of seasonal influenza vaccination for both the cohort and cross-section populations. For both populations, we are reporting the cumulative vaccination rates by week (as a proportion of registered patients), and a tabular summary of vaccination rates, disaggregated by age group, surveillance method, risk groups, and concomitant vaccines. The tabular summary is reported across the two groups outlined in the methods: vaccinated patients divided across vaccine brand (GSK and non-GSK), and all registered patients divided across vaccination status. These will be the denominators that will be used to calculate the AEI rate.

The cumulative vaccination rates across the study weeks (week 35 to 49; there were no vaccinations in week 35) are shown in Figure 14. The final vaccination rate for the cross-section population (19.6, 95%CI 19.3-19.7, Table 8) was lower than that for the cohort (20.7%, 95%CI 20.4-21.0, Table 9). About three-quarters (77.2% in the cross-section and 76.8% in the cohort) of the vaccinated patients received a non-GSK vaccine while the rest (22.8% in the cross-section and 23.2% in the cohort) received a GSK vaccine.

Figure 14 - Cumulative vaccination by week for the cross-section and the cohort, with confidence intervals



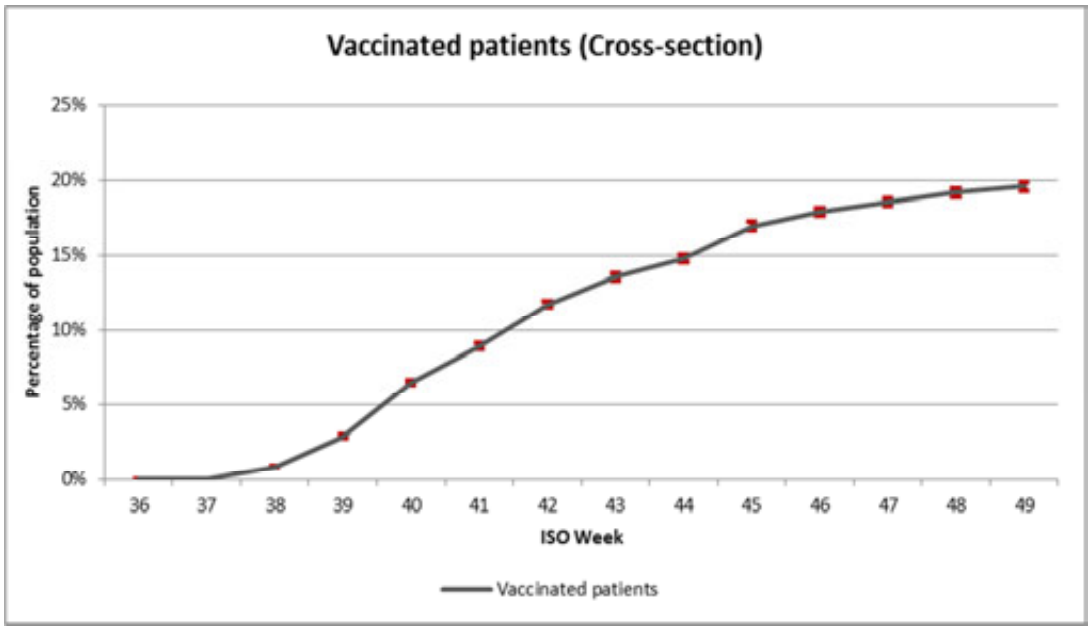


Table 8 – Tabular summary of vaccination status for the cross-section, with confidence intervals

Vaccination status (Cross section)								
	Vaccinated (Non-GSK)		*Vaccinated (GSK)*		*Vaccinated (All)*		*Non vaccinated*	
Total	12194		3597		15791		64844	
	77.22%		22.78%		19.58%		80.42%	
	76.56%	77.87%	22.13%	23.44%	19.31%	19.86%	80.14%	80.69%

Table 9– Tabular summary of vaccination status for the cohort, with confidence intervals

Vaccination status (Cohort)								
	Vaccinated (Non-GSK)		*Vaccinated (GSK)*		*Vaccinated (All)*		*Non vaccinated*	
Total	11367		3434		14801		56606	
	76.80%		23.20%		20.73%		79.27%	
	76.12%	77.47%	22.53%	23.88%	20.43%	21.03%	78.97%	79.57%

Table 10 - Table 12 include a disaggregation of the vaccination status of the cross-section population by age group, surveillance method, vaccine brand, and concomitant vaccines, and Table 13 -

Table 15 include the same disaggregation for the cohort population. The highest vaccination uptake rates were found in patients aged over 65 years old, both in the cohort and in the cross-section populations. These patients are strongly targeted by GPs to reach national targets of vaccine coverage in risk groups. All patients who had a concomitant vaccine administered (against pneumococcal disease and/or shingles) also received a seasonal influenza vaccine.

We disaggregated the vaccinated group by the different CMO high risk groups recommended for influenza vaccination (Table 16 Table 17). The vaccination rates for the people aged over 65, children aged under 4, and pregnant women were slightly lower than the national rates, for both the cohort and the cross-section populations[40]. There was a majority of vaccinated patients for Coronary Heart Disease, Chronic Kidney Disease, Diabetes, Immunosuppressed, Neurological disease and in people over 65 years old for both the cohort and the cross-section populations.

***Table 10* – Tabular summary of vaccination status in the cross section by age group, with confidence intervals**

Vaccination status (Cross section)								
Age Group	***Vaccinated (Non-GSK)***		***Vaccinated (GSK)***		***Vaccinated (All)***		***Non vaccinated***	
<1yr	0		0		0		0	
	N/A		N/A		N/A		N/A	
	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
1-4yrs	388		52		440		2440	
	88.18%		11.82%		15.28%		84.72%	
	85.00%	91.14%	8.86%	15.00%	13.96%	16.60%	83.40%	86.04%
5-14yrs	1210		57		1267		6770	
	95.50%		4.50%		15.76%		84.24%	
	94.32%	96.61%	3.39%	5.68%	14.97%	16.56%	83.44%	85.03%
15-24yrs	258		69		327		10152	
	78.90%		21.10%		3.12%		96.88%	
	74.31%	83.18%	16.82%	25.69%	2.80%	3.45%	96.55%	97.20%
25-44yrs	932		194		1126		19111	
	82.77%		17.23%		5.56%		94.44%	
	80.55%	84.99%	15.01%	19.45%	5.25%	5.88%	94.12%	94.75%
45-64yrs	2125		597		2722		19019	
	78.07%		21.93%		12.52%		87.48%	
	76.49%	79.61%	20.39%	23.51%	12.08%	12.96%	87.04%	87.92%
65-74yrs	3396		1136		4532		4424	
	74.93%		25.07%		50.60%		49.40%	
	73.68%	76.19%	23.81%	26.32%	49.56%	51.64%	48.36%	50.44%
75-84yrs	2559		1010		3569		1948	
	71.70%		28.30%		64.69%		35.31%	
	70.22%	73.19%	26.81%	29.78%	63.42%	65.94%	34.06%	36.58%
85+yrs	1326		482		1808		980	
	73.34%		26.66%		64.85%		35.15%	
	71.29%	75.39%	24.61%	28.71%	63.06%	66.61%	33.39%	36.94%

Table 11– Tabular summary of vaccination status in the cross section by surveillance method, with confidence intervals

Vaccination status (Cross section)								
Surveillance method	***Vaccinated (Non-GSK)***		***Vaccinated (GSK)***		***Vaccinated (All)***		***Non vaccinated***	
Enhanced passive arm (n=3 GP practices)	3607		3597		7204		0	
	50.07%		49.93%		100.00%		0.00%	
	48.92%	51.22%	48.78%	51.08%	N/A	N/A	N/A	N/A
EHR data mining arm (n=6 GP practices)	8587		0		8587		64844	
	100.00%		0.00%		11.69%		88.31%	
	N/A	N/A	N/A	N/A	11.46%	11.93%	88.07%	88.54%

Table 12 – Tabular summary of vaccination status in the cross section by concomitant vaccines, with confidence intervals

Vaccination status (Cross section)								
Concomitant vaccines	***Vaccinated (Non-GSK)***		***Vaccinated (GSK)***		***Vaccinated (All)***		***Non vaccinated***	
Any concomitant vaccine	210		0		210		0	
	100.00%		0.00%		100.00%		0.00%	
	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Concomitant pneumococcal	140		0		140		0	
	100.00%		0.00%		100.00%		0.00%	
	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Concomitant shingles	71		0		71		0	
	100.00%		0.00%		100.00%		0.00%	
	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table 13 – Tabular summary of vaccination status in the cohort by age group, with confidence intervals

Vaccination status (Cohort)				
Age Group	*Vaccinated (Non-GSK)*	*Vaccinated (GSK)*	*Vaccinated (All)*	*Non vaccinated*
<1yr	0	0	0	0
	N/A	N/A	N/A	N/A
	N/A N/A	N/A N/A	N/A N/A	N/A N/A
1-4yrs	330	40	370	1262
	89.19%	10.81%	22.67%	77.33%
	85.95% 92.16%	7.84% 14.05%	20.65% 24.69%	75.31% 79.35%
5-14yrs	1122	51	1173	6190
	95.65%	4.35%	15.93%	84.07%
	94.46% 96.76%	3.24% 5.54%	15.10% 16.77%	83.23% 84.90%
15-24yrs	221	49	270	7975
	81.85%	18.15%	3.27%	96.73%
	77.04% 86.30%	13.70% 22.96%	2.90% 3.66%	96.34% 97.10%
25-44yrs	785	172	957	16273
	82.03%	17.97%	5.55%	94.45%
	79.52% 84.43%	15.57% 20.48%	5.22% 5.90%	94.10% 94.78%
45-64yrs	2019	560	2579	17930
	78.29%	21.71%	12.57%	87.43%
	76.70% 79.88%	20.12% 23.30%	12.12% 13.03%	86.97% 87.88%
65-74yrs	3242	1111	4353	4206
	74.48%	25.52%	50.86%	49.14%
	73.17% 75.76%	24.24% 26.83%	49.80% 51.92%	48.08% 50.20%
75-84yrs	2426	988	3414	1864
	71.06%	28.94%	64.68%	35.32%
	69.54% 72.58%	27.42% 30.46%	63.40% 65.97%	34.03% 36.60%
85+yrs	1222	463	1685	906
	72.52%	27.48%	65.03%	34.97%
	70.39% 74.66%	25.34% 29.61%	63.18% 66.85%	33.15% 36.82%

***Table 14*– Tabular summary of vaccination status in the cohort by surveillance method, with confidence intervals, the enhanced passive surveillance practices had higher immunisation rates**

Vaccination status (Cohort)								
Surveillance method	***Vaccinated (Non-GSK)***		***Vaccinated (GSK)***		***Vaccinated (All)***		***Non vaccinated***	
Enhanced passive arm (n=3 GP practices)	3342		3434		6776		0	
	49.32%		50.68%		100.00%		0.00%	
	48.13%	50.52%	49.48%	51.87%	N/A	N/A	N/A	N/A
EHR data mining arm (n=6 GP practices)	8025		0		8025		56606	
	100.00%		0.00%		12.42%		87.58%	
	N/A	N/A	N/A	N/A	12.16%	12.67%	87.33%	87.84%

***Table 15* – Tabular summary of vaccination status in the cohort by concomitant vaccines, with confidence intervals.**

Vaccination status (Cohort)								
Concomitant vaccines	***Vaccinated (Non-GSK)***		***Vaccinated (GSK)***		***Vaccinated (All)***		***Non vaccinated***	
Any concomitant vaccine	195		0		195		0	
	100.00%		0.00%		100.00%		0.00%	
	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Concomitant pneumococcal	130		0		130		0	
	100.00%		0.00%		100.00%		0.00%	
	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Concomitant shingles	66		0		66		0	
	100.00%		0.00%		100.00%		0.00%	
	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table 16 – **Tabular summary of vaccination status in the cross section by risk group**

Vaccination status (Cross section)				
Risk Group	***Vaccinated (Non-GSK)***	***Vaccinated (GSK)***	***Vaccinated (All)***	***Non vaccinated***
Any risk group	10342	3284	13626	19807
	75.90%	24.10%	40.76%	59.24%
	75.18% 76.62%	23.38% 24.82%	40.23% 41.28%	58.72% 59.77%
Asthma	1578	293	1871	2985
	84.34%	15.66%	38.53%	61.47%
	82.68% 85.94%	14.06% 17.32%	37.17% 39.91%	60.09% 62.83%
Chronic Respiratory Disease	2523	549	3072	4155
	82.13%	17.87%	42.51%	57.49%
	80.76% 83.46%	16.54% 19.24%	41.37% 43.64%	56.36% 58.63%
Chronic Heart Disease	2291	673	2964	1663
	77.29%	22.71%	64.06%	35.94%
	75.78% 78.78%	21.22% 24.22%	62.68% 65.44%	34.56% 37.32%
Chronic Kidney Disease	1171	613	1784	728
	65.64%	34.36%	71.02%	28.98%
	63.45% 67.83%	32.17% 36.55%	69.23% 72.77%	27.23% 30.77%
Chronic Liver Disease	895	301	1196	1457
	74.83%	25.17%	45.08%	54.92%
	72.32% 77.26%	22.74% 27.68%	43.20% 46.97%	53.03% 56.80%
Diabetes	1668	636	2304	850
	72.40%	27.60%	73.05%	26.95%
	70.57% 74.22%	25.78% 29.43%	71.50% 74.60%	25.40% 28.50%
Immunosuppression	186	32	218	118
	85.32%	14.68%	64.88%	35.12%
	80.28% 89.91%	10.09% 19.72%	59.82% 69.94%	30.06% 40.18%
Chronic Neurological Disease	1327	428	1755	1268
	75.61%	24.39%	58.05%	41.95%
	73.62% 77.61%	22.39% 26.38%	56.30% 59.81%	40.19% 43.70%
Asplenia	146	36	182	253
	80.22%	19.78%	41.84%	58.16%
	74.18% 85.71%	14.29% 25.82%	37.24% 46.44%	53.56% 62.76%
Obesity	417	118	535	826
	77.94%	22.06%	39.31%	60.69%
	74.39% 81.50%	18.50% 25.61%	36.74% 41.88%	58.12% 63.26%
Pregnancy	490	98	588	4117
	83.33%	16.67%	12.50%	87.50%
	80.27% 86.22%	13.78% 19.73%	11.56% 13.45%	86.55% 88.44%
Under 4 years old	388	52	440	2440
	88.18%	11.82%	15.28%	84.72%
	85.00% 91.14%	8.86% 15.00%	13.96% 16.60%	83.40% 86.04%
Over 65 years old	7281	2628	9909	7352
	73.48%	26.52%	57.41%	42.59%
	72.61% 74.35%	25.65% 27.39%	56.67% 58.14%	41.86% 43.33%

Table 17 – **Tabular summary of vaccination status in the cohort by risk group**

Vaccination status (Cohort)				
Risk Group	***Vaccinated (Non-GSK)***	***Vaccinated (GSK)***	***Vaccinated (All)***	***Non vaccinated***
Any risk group	9685	3154	12839	17267
	75.43%	24.57%	42.65%	57.35%
	74.69% 76.17%	23.83% 25.31%	42.09% 43.20%	56.80% 57.91%
Asthma	1494	281	1775	2736
	84.17%	15.83%	39.35%	60.65%
	82.48% 85.86%	14.14% 17.52%	37.93% 40.77%	59.23% 62.07%
Chronic Respiratory Disease	2391	532	2923	3787
	81.80%	18.20%	43.56%	56.44%
	80.40% 83.20%	16.80% 19.60%	42.37% 44.75%	55.25% 57.63%
Chronic Heart Disease	2158	655	2813	1531
	76.72%	23.28%	64.76%	35.24%
	75.15% 78.28%	21.72% 24.85%	63.33% 66.18%	33.82% 36.67%
Chronic Kidney Disease	1114	592	1706	677
	65.30%	34.70%	71.59%	28.41%
	63.01% 67.53%	32.47% 36.99%	69.79% 73.39%	26.61% 30.21%
Chronic Liver Disease	847	288	1135	1334
	74.63%	25.37%	45.97%	54.03%
	72.07% 77.09%	22.91% 27.93%	44.03% 47.95%	52.05% 55.97%
Diabetes	1588	614	2202	789
	72.12%	27.88%	73.62%	26.38%
	70.25% 73.98%	26.02% 29.75%	72.05% 75.19%	24.81% 27.95%
Immunosuppression	178	30	208	106
	85.58%	14.42%	66.24%	33.76%
	80.77% 90.38%	9.62% 19.23%	60.83% 71.34%	28.66% 39.17%
Chronic Neurological Disease	1218	403	1621	1145
	75.14%	24.86%	58.60%	41.40%
	73.04% 77.24%	22.76% 26.96%	56.76% 60.45%	39.55% 43.24%
Asplenia	138	36	174	229
	79.31%	20.69%	43.18%	56.82%
	72.99% 85.06%	14.94% 27.01%	38.46% 48.14%	51.86% 61.54%
Obesity	395	113	508	740
	77.76%	22.24%	40.71%	59.29%
	74.02% 81.30%	18.70% 25.98%	37.98% 43.43%	56.57% 62.02%
Pregnancy	412	86	498	3663
	82.73%	17.27%	11.97%	88.03%
	79.32% 85.94%	14.06% 20.68%	10.98% 12.95%	87.05% 89.02%
Under 4 years old	330	40	370	1262
	89.19%	10.81%	22.67%	77.33%
	85.95% 92.16%	7.84% 14.05%	20.65% 24.69%	75.31% 79.35%
Over 65 years old	6890	2562	9452	6976
	72.89%	27.11%	57.54%	42.46%
	72.00% 73.78%	26.22% 28.00%	56.78% 58.29%	41.71% 43.22%

8. Safety data

8.1. Overview of safety data reporting

In this section we report the key data required by the EMA in detail, namely the AEIs. The particular focus is demonstrating we can provide data from the weekly reports (weekly cross-sectional data). We also report IDE rate for non-vaccinated patients because we feel there is a dearth of data about background rates of these conditions. Without background data, particularly week-on-week fluctuation, it may be difficult to differentiate a signal due to an IDE from that from an AEI. Further disaggregated data, severity data, and statistical analysis is provided for the cohort population.

8.2. Frequency reporting

We report the AEI rates for specific conditions and their broad category, for both the cohort and the cross-section. For the cross-section, we are adding AEIs occurring up to week 49, but we also reference the week by week data seen in the weekly reports (Appendix A). We report rates across the same two groups as the vaccine exposure, where patients with an AEI are counted differently. For all vaccinated patients, where we compare across vaccine brand, we count only patients with an AEI occurring 14 days post-vaccination. For all registered patients, where we compare across vaccinations status, we count patients with an AEI happening at any point during the study period.

It must be noted that the week-on-week rates in the weekly reports only do one comparison of rates, between vaccinated and non-vaccinated. For the vaccinated, only patients with AEIs occurring that week and within 14 days post-vaccination are counted as a proportion of all patients vaccinated in the preceding 14 days. For the non-vaccinated, all patients with AEIs occurring that week (minus those patients with an AEI happening within 14 days post-vaccination) are counted as a proportion of all registered patients (minus patients vaccinated to date). Given the differing denominators, an attempt should not be made to directly compare the rates of the two charts.

Both in the cohort and in the cross-section, there was a small number of AEIs reported for non-GSK (n=366, 3.00% in the cross section, and n=333, 2.93% in the cohort) and GSK (n=94, 2.61% in the cross section, and n=92, 2.68% in the cohort) vaccine recipients during the 14-day window following the seasonal influenza vaccination (Table 18 Table 19). This is reflected in the weekly reports, where most weeks show low numbers in the tabular summary for vaccinated patients, even if the rates appear large (the rates in the weekly reports are calculated per 100,000 patients).

The rate of AEIs/IDEs presenting at any point in the study period for the vaccinated population was 12.1% (95%CI 11.6-12.6, n=1907) and 11.9% (95%CI 11.4-12.4, n=1761) in the cohort. For the non-vaccinated population, this rate was 5.7% (95%CI 5.5-5.9, n=3679) in the cross-section and 5.2% in the cohort (95%CI 5.0-5.4, n=2939); all of these results are shown in Table 18 andTable 19. The non-vaccinated and vaccinated groups were not matched on many important factors, so it is unsurprising that the crude rates are different. The data in non-vaccinated subjects were provided principally as background rates to help interpret the surveillance data.

Table 18– Tabular summary of all adverse events for the cross-section by vaccination status, with confidence intervals

	AEI/IDE							
	AEI within 14-day post-vaccination				AEI/IDE at any time			
Any Adverse Event	*Vaccinated (Non-GSK)*		*Vaccinated (GSK)*		*Vaccinated*		*Non vaccinated*	
Any Adverse Event	366		94		1907		3679	
	3.00%		2.61%		12.08%		5.67%	
	2.71%	3.30%	2.11%	3.14%	11.57%	12.59%	5.50%	5.85%

Table 19– Tabular summary of all adverse events for the cohort by vaccination status, with confidence intervals

	AEI/IDE							
	AEI within 14-day post-vaccination				AEI/IDE at any time			
Any Adverse Event	*Vaccinated (Non-GSK)*		*Vaccinated (GSK)*		*Vaccinated*		*Non vaccinated*	
Any Adverse Event	333		92		1761		2939	
	2.93%		2.68%		11.90%		5.19%	
	2.62%	3.25%	2.15%	3.23%	11.38%	12.42%	5.01%	5.38%

Table 20 - Table 28 give a detailed break-down of rates for each specific AEI/IDE, and their broader category for the cross-section. Table 29 - Table 37 provide the same rates for the cohort. They are organised using the same four columns. The first two provide AEI numbers occurring in a 14-day window post-vaccination, their rate (against denominators from the tabular summary of vaccination in Table 5) and 95% confidence intervals, comparing GSK and non-GSK influenza vaccine. The third and fourth columns compare AEI numbers occurring at any point in the study period, their rate (using the denominators in Table 5) and 95% confidence intervals, comparing vaccinated and non-vaccinated.

In the cross-section population, respiratory (0.96% for non-GSK and 0.89% for GSK vaccines), fever/pyrexia (0.80% for non-GSK and 0.67% for GSK vaccines), and musculoskeletal (0.52% for non-GSK and 0.89% for GSK vaccines) AEIs were the most common. This is consistent with the findings from the weekly reports, where these three categories of AEIs are routinely reported as the most frequent. Similarly, these three conditions are also the highest in the cohort population: respiratory (0.95% for non-GSK and 0.90% for GSK vaccines), fever/pyrexia (0.77% for non-GSK and 0.67% for GSK vaccines), and musculoskeletal (0.48% for non-GSK and 0.93% for GSK vaccines).

The higher musculoskeletal rates in the GSK-vaccinated population are entirely driven by the specific condition of muscle aches/myalgia (32 cases both in the cohort and in the cross-sections). Similar to this, the rate of local erythema, while not very high compared to other conditions, is higher in the cohort and cross-section populations vaccinated with a GSK vaccine (0.17% in the cross-section and the cohort, n=6) compared to those vaccinated with a non-GSK vaccine (0.02% in the cross section, 0.03% in the cohort, n=3). However, the latter should be

treated with caution because GSK vaccine was only in the enhanced passive surveillance (yellow card) arm and this AEI was reported more in this arm.

Table 20 - Tabular summary of respiratory adverse events (including specific conditions) for the cross-section by vaccination status, with confidence intervals

	AEI/IDE			
	AEI within 14-day post-vaccination		AEI/IDE at any time	
Respiratory / Miscellaneous	*Vaccinated (Non-GSK)*	*Vaccinated (GSK)*	*Vaccinated*	*Non vaccinated*
Conjunctivitis	14	1	84	200
	0.11%	0.03%	0.53%	0.31%
	0.06% 0.18%	N/A N/A	0.42% 0.65%	0.27% 0.35%
Rhinorrhoea	0	5	12	4
	0.00%	0.14%	0.08%	0.01%
	N/A N/A	N/A N/A	0.04% 0.12%	N/A N/A
Nasal congestion	6	8	48	82
	0.05%	0.22%	0.30%	0.13%
	N/A N/A	0.08% 0.39%	0.22% 0.39%	0.10% 0.15%
Epistaxis	6	0	26	43
	0.05%	0.00%	0.16%	0.07%
	N/A N/A	N/A N/A	0.11% 0.23%	0.05% 0.09%
Coryza	2	0	13	24
	0.02%	0.00%	0.08%	0.04%
	N/A N/A	N/A N/A	N/A N/A	0.02% 0.05%
Cough	73	20	461	644
	0.60%	0.56%	2.92%	0.99%
	0.47% 0.74%	N/A N/A	2.66% 3.19%	0.92% 1.07%
Oropharyngeal pain	10	7	56	210
	0.08%	0.19%	0.35%	0.32%
	N/A N/A	N/A N/A	0.27% 0.45%	0.28% 0.37%
Hoarseness	1	0	10	16
	0.01%	0.00%	0.06%	0.02%
	N/A N/A	N/A N/A	N/A N/A	0.01% 0.04%
Wheezing	12	2	50	87
	0.10%	0.06%	0.32%	0.13%
	N/A N/A	N/A N/A	0.23% 0.41%	0.11% 0.16%
Any respiratory / miscellaneous	117	32	709	1246
	0.96%	0.89%	4.49%	1.92%
	0.79% 1.14%	0.58% 1.20%	4.17% 4.81%	1.82% 2.03%

Table 21 - Tabular summary of gastrointestinal adverse events (including specific conditions) for the cross-section by vaccination status, with confidence intervals

	AEI within 14-day post-vaccination		AEI/IDE at any time	
Gastrointestinal	***Vaccinated (Non-GSK)***	***Vaccinated (GSK)***	***Vaccinated***	***Non vaccinated***
Decreased appetite	3	0	16	11
	0.02%	0.00%	0.10%	0.02%
	N/A N/A	N/A N/A	0.06% 0.15%	N/A N/A
Nausea	6	1	25	64
	0.05%	0.03%	0.16%	0.10%
	0.02% 0.09%	N/A N/A	0.10% 0.22%	0.08% 0.12%
Vomiting	5	0	42	78
	0.04%	0.00%	0.27%	0.12%
	0.01% 0.08%	N/A N/A	0.19% 0.35%	0.09% 0.15%
Diarrhoea	17	1	144	161
	0.14%	0.03%	0.91%	0.25%
	N/A N/A	N/A N/A	0.77% 1.06%	0.21% 0.29%
Any gastrointestinal	29	2	219	304
	0.24%	0.06%	1.39%	0.47%
	0.16% 0.33%	N/A N/A	1.21% 1.57%	0.42% 0.52%

Table 22 – Tabular summary of fever/pyrexia adverse events (including specific conditions) for the cross-section by vaccination status, with confidence intervals

	AEI/IDE			
	AEI within 14-day post-vaccination		AEI/IDE at any time	
Fever / Pyrexia	***Vaccinated (Non-GSK)***	***Vaccinated (GSK)***	***Vaccinated***	***Non vaccinated***
Fever	16	7	56	113
	0.13%	0.19%	0.35%	0.17%
	0.07% 0.20%	N/A N/A	0.27% 0.45%	0.14% 0.21%
Fever with temperature	82	18	440	907
	0.67%	0.50%	2.79%	1.40%
	0.53% 0.82%	N/A N/A	2.53% 3.05%	1.31% 1.49%
Any fever / pyrexia	97	24	487	1003
	0.80%	0.67%	3.08%	1.55%
	0.64% 0.96%	N/A N/A	2.82% 3.36%	1.45% 1.64%

Table 23 – Tabular summary of sensitivity/anaphylaxis adverse events (including specific conditions) for the cross-section by vaccination status, with confidence intervals

	AEI/IDE							
	AEI within 14-day post-vaccination				AEI/IDE at any time			
Sensitivity / Anaphylaxis	*Vaccinated (Non-GSK)*		*Vaccinated (GSK)*		*Vaccinated*		*Non vaccinated*	
Hypersensitivity reactions	4		0		22		47	
	0.03%		0.00%		0.14%		0.07%	
	N/A	N/A	N/A	N/A	0.08%	0.20%	0.05%	0.09%
Anaphylactic reactions	0		1		1		3	
	0.00%		0.03%		0.01%		0.00%	
	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Facial oedema	1		0		2		3	
	0.01%		0.00%		0.01%		0.00%	
	N/A	N/A	N/A	N/A	N/A	N/A	N	N/A
Any sensitivity / anaphylaxis	5		1		24		53	
	0.04%		0.03%		0.15%		0.08%	
	N/A	N/A	N/A	N/A	0.09%	0.22%	0.06%	0.10%

Table 24 – Tabular summary of rash adverse events (including specific conditions) for the cross-section by vaccination status, with confidence intervals

	AEI/IDE							
	AEI within 14-day post-vaccination				AEI/IDE at any time			
Rash	*Vaccinated (Non-GSK)*		*Vaccinated (GSK)*		*Vaccinated*		*Non vaccinated*	
Rash	0		1		2		0	
	0.00%		0.03%		0.01%		0.00%	
	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Generalised rash	24		6		157		363	
	0.20%		0.17%		0.99%		0.56%	
	0.12%	0.28%	0.06%	0.31%	0.84%	1.15%	0.50%	0.62%
Any rash	24		7		159		363	
	0.20%		0.19%		1.01%		0.56%	
	0.12%	0.28%	0.06%	0.36%	0.85%	1.17%	0.50%	0.62%

Table 25 – Tabular summary of general symptoms adverse events (including specific conditions) for the cross-section by vaccination status, with confidence intervals

	AEI/IDE							
	AEI within 14-day post-vaccination				AEI/IDE at any time			
General non-specific symptoms	*Vaccinated (Non-GSK)*		*Vaccinated (GSK)*		*Vaccinated*		*Non vaccinated*	
Irritability	0		0		2		9	
	0.00%		0.00%		0.01%		0.01%	
	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drowsiness	2		0		14		8	
	0.02%		0.00%		0.09%		0.01%	
	N/A	N/A	N/A	N/A	0.04%	0.14%	0.00%	0.02%
Fatigue	16		7		81		145	
	0.13%		0.19%		0.51%		0.22%	
	N/A	N/A	N/A	N/A	0.41%	0.63%	0.19%	0.26%
Any general symptom	23		8		132		217	
	0.19%		0.22%		0.84%		0.33%	
	N/A	N/A	N/A	N/A	0.70%	0.98%	0.29%	0.38%

Table 26 – Tabular summary of neurological adverse events (including specific conditions) for the cross-section by vaccination status, with confidence intervals

	AEI/IDE							
	AEI within 14-day post-vaccination				AEI/IDE at any time			
Neurological	*Vaccinated (Non-GSK)*		*Vaccinated (GSK)*		*Vaccinated*		*Non vaccinated*	
Peripheral tremor	3		0		7		8	
	0.02%		0.00%		0.04%		0.01%	
	N/A	N/A	N/A	N/A	N/A	N/A	0.00%	0.02%
Guillain-Barre Syndrome (GBS)	0		0		1		1	
	0.00%		0.00%		0.01%		0.00%	
	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Seizure / Febrile convulsions	2		0		7		16	
	0.02%		0.00%		0.04%		0.02%	
	N/A	N/A	N/A	N/A	0.01%	0.08%	N/A	N/A
Headache	29		6		134		390	
	0.24%		0.17%		0.85%		0.60%	
	0.16%	0.33%	N/A	N/A	0.71%	0.99%	0.54%	0.66%
Any neurological	34		6		149		414	
	0.28%		0.17%		0.94%		0.64%	
	0.19%	0.38%	N/A	N/A	0.80%	1.10%	0.58%	0.70%

Table 27 – Tabular summary of musculoskeletal adverse events (including specific conditions) for the cross-section by vaccination status, with confidence intervals

	AEI/IDE							
	AEI within 14-day post-vaccination				AEI/IDE at any time			
Musculoskeletal	*Vaccinated (Non-GSK)*		*Vaccinated (GSK)*		*Vaccinated*		*Non vaccinated*	
Muscle aches / myalgia	63		32		378		598	
	0.52%		0.89%		2.39%		0.92%	
	0.39%	0.65%	0.58%	1.20%	2.16%	2.63%	0.85%	1.00%
Arthropathy	0		0		1		0	
	0.00%		0.00%		0.01%		0.00%	
	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Any musculoskeletal	63		32		378		598	
	0.52%		0.89%		2.39%		0.92%	
	0.39%	0.65%	0.58%	1.20%	2.16%	2.63%	0.85%	1.00%

Table 28– Tabular summary of local symptoms adverse events (including specific conditions) for the cross-section by vaccination status, with confidence intervals

	AEI/IDE							
	AEI within 14-day post-vaccination				AEI/IDE at any time			
Local symptoms	*Vaccinated (Non-GSK)*		*Vaccinated (GSK)*		*Vaccinated*		*Non vaccinated*	
Local erythema	3		6		12		0	
	0.02%		0.17%		0.08%		0.00%	
	0.00%	0.06%	N/A	N/A	0.04%	0.12%	N/A	N/A
Any local symptom	3		6		12		0	
	0.02%		0.17%		0.08%		0.00%	
	0.00%	0.06%	N/A	N/A	0.04%	0.12%	N/A	N/A

Table 29 – Tabular summary of respiratory adverse events (including specific conditions) for the cohort by vaccination status, with confidence intervals

	AEI/IDE			
	AEI within 14-day post-vaccination		AEI/IDE at any time	
Respiratory / Miscellaneous	*Vaccinated (Non-GSK)*	*Vaccinated (GSK)*	*Vaccinated*	*Non vaccinated*
Conjunctivitis	13	1	80	143
	0.11%	0.03%	0.54%	0.25%
	0.05% 0.18%	0.00% 0.09%	0.43% 0.66%	0.21% 0.30%
Rhinorrhoea	0	5	11	4
	0.00%	0.15%	0.07%	0.01%
	N/A N/A	0.03% 0.29%	0.03% 0.12%	0.00% 0.01%
Nasal congestion	6	8	48	63
	0.05%	0.23%	0.32%	0.11%
	0.02% 0.10%	0.09% 0.41%	0.24% 0.42%	0.08% 0.14%
Epistaxis	5	0	25	35
	0.04%	0.00%	0.17%	0.06%
	0.01% 0.09%	N/A N/A	0.11% 0.24%	0.04% 0.08%
Coryza	2	0	11	13
	0.02%	0.00%	0.07%	0.02%
	0.00% 0.04%	N/A N/A	0.03% 0.12%	0.01% 0.04%
Cough	68	19	422	495
	0.60%	0.55%	2.85%	0.87%
	0.46% 0.75%	0.32% 0.82%	2.59% 3.12%	0.80% 0.95%
Oropharyngeal pain	8	7	51	178
	0.07%	0.20%	0.34%	0.31%
	0.03% 0.12%	0.06% 0.38%	0.26% 0.44%	0.27% 0.36%
Hoarseness	1	0	10	11
	0.01%	0.00%	0.07%	0.02%
	0.00% 0.03%	N/A N/A	0.03% 0.11%	0.01% 0.03%
Wheezing	12	2	45	68
	0.11%	0.06%	0.30%	0.12%
	0.05% 0.17%	0.00% 0.15%	0.22% 0.40%	0.09% 0.15%
Any respiratory / miscellaneous	108	31	652	965
	0.95%	0.90%	4.41%	1.70%
	0.77% 1.13%	0.61% 1.22%	4.08% 4.74%	1.60% 1.81%

Table 30– Tabular summary of gastrointestinal adverse events (including specific conditions for the cohort by vaccination status, with confidence intervals

	AEI/IDE			
	AEI within 14-day post-vaccination		AEI/IDE at any time	
Gastrointestinal	*Vaccinated (Non-GSK)*	*Vaccinated (GSK)*	*Vaccinated*	*Non vaccinated*
Decreased appetite	3	0	15	10
	0.03%	0.00%	0.10%	0.02%
	0.00% 0.06%	N/A N/A	0.05% 0.16%	0.01% 0.03%
Nausea	5	1	24	57
	0.04%	0.03%	0.16%	0.10%
	0.01% 0.09%	0.00% 0.09%	0.10% 0.23%	0.08% 0.13%
Vomiting	4	0	36	47
	0.04%	0.00%	0.24%	0.08%
	0.01% 0.07%	N/A N/A	0.17% 0.32%	0.06% 0.11%
Diarrhoea	14	1	133	121
	0.12%	0.03%	0.90%	0.21%
	0.06% 0.19%	0.00% 0.09%	0.75% 1.05%	0.18% 0.25%
Any gastrointestinal	24	2	201	232
	0.21%	0.06%	1.36%	0.41%
	0.13% 0.30%	0.00% 0.15%	1.18% 1.55%	0.36% 0.46%

Table 31 – Tabular summary of fever/pyrexia adverse events (including specific conditions) for the cohort by vaccination status, with confidence intervals

	AEI/IDE			
	AEI within 14-day post-vaccination		AEI/IDE at any time	
Fever / Pyrexia	*Vaccinated (Non-GSK)*	*Vaccinated (GSK)*	*Vaccinated*	*Non vaccinated*
Fever	16	7	52	86
	0.14%	0.20%	0.35%	0.15%
	0.08% 0.21%	0.06% 0.38%	0.26% 0.45%	0.12% 0.19%
Fever with temperature	72	17	393	662
	0.63%	0.50%	2.66%	1.17%
	0.49% 0.78%	0.26% 0.73%	2.40% 2.92%	1.08% 1.26%
Any fever / pyrexia	87	23	438	739
	0.77%	0.67%	2.96%	1.31%
	0.61% 0.93%	0.41% 0.96%	2.69% 3.24%	1.21% 1.40%

Table 32– Tabular summary of sensitivity/anaphylaxis adverse events (including specific conditions) for the cohort by vaccination status, with confidence intervals

	AEI/IDE							
	AEI within 14-day post-vaccination				AEI/IDE at any time			
Sensitivity / Anaphylaxis	*Vaccinated (Non-GSK)*		*Vaccinated (GSK)*		*Vaccinated*		*Non vaccinated*	
Hypersensitivity reactions	4		0		15		32	
	0.04%		0.00%		0.10%		0.06%	
	0.01%	0.07%	N/A	N/A	0.05%	0.16%	0.04%	0.08%
Anaphylactic reactions	0		0		0		3	
	0.00%		0.00%		0.00%		0.01%	
	N/A	N/A	N/A	N/A	N/A	N/A	0.00%	0.01%
Facial oedema	1		0		2		2	
	0.01%		0.00%		0.01%		0.00%	
	0.00%	0.03%	N/A	N/A	0.00%	0.03%	0.00%	0.01%
Any sensitivity / anaphylaxis	5		0		16		37	
	0.04%		0.00%		0.11%		0.07%	
	0.01%	0.09%	N/A	N/A	0.06%	0.16%	0.05%	0.09%

Table 33 – Tabular summary of rash adverse events (including specific conditions) for the cohort by vaccination status, with confidence intervals

	AEI/IDE							
	AEI within 14-day post-vaccination				AEI/IDE at any time			
Rash	*Vaccinated (Non-GSK)*		*Vaccinated (GSK)*		*Vaccinated*		*Non vaccinated*	
Rash	0		1		2		0	
	0.00%		0.03%		0.01%		0.00%	
	N/A	N/A	0.00%	0.09%	0.00%	0.03%	N/A	N/A
Generalised rash	24		6		148		250	
	0.21%		0.17%		1.00%		0.44%	
	0.13%	0.30%	0.06%	0.32%	0.84%	1.16%	0.39%	0.50%
Any rash	24		7		150		250	
	0.21%		0.20%		1.01%		0.44%	
	0.13%	0.30%	0.06%	0.38%	0.86%	1.18%	0.39%	0.50%

Table 34 – Tabular summary of general symptoms adverse events (including specific conditions) for the cohort by vaccination status, with confidence intervals

	AEI/IDE			
	AEI within 14-day post-vaccination		AEI/IDE at any time	
General non-specific symptoms	*Vaccinated (Non-GSK)*	*Vaccinated (GSK)*	*Vaccinated*	*Non vaccinated*
Irritability	0	0	2	7
	0.00%	0.00%	0.01%	0.01%
	N/A N/A	N/A N/A	0.00% 0.03%	0.00% 0.02%
Drowsiness	2	0	12	7
	0.02%	0.00%	0.08%	0.01%
	0.00% 0.04%	N/A N/A	0.04% 0.13%	0.00% 0.02%
Fatigue	16	7	77	127
	0.14%	0.20%	0.52%	0.22%
	0.08% 0.21%	0.06% 0.38%	0.41% 0.64%	0.19% 0.26%
Any general symptom	23	8	126	187
	0.20%	0.23%	0.85%	0.33%
	0.12% 0.29%	0.09% 0.41%	0.71% 1.00%	0.28% 0.38%

Table 35 – Tabular summary of neurological adverse events (including specific conditions) for the cohort by vaccination status, with confidence intervals

	AEI/IDE			
	AEI within 14-day post-vaccination		AEI/IDE at any time	
Neurological	*Vaccinated (Non-GSK)*	*Vaccinated (GSK)*	*Vaccinated*	*Non vaccinated*
Peripheral tremor	3	0	6	8
	0.03%	0.00%	0.04%	0.01%
	0.00% 0.06%	N/A N/A	0.01% 0.07%	0.01% 0.02%
Guillain-Barre Syndrome (GBS)	0	0	1	1
	0.00%	0.00%	0.01%	0.00%
	N/A N/A	N/A N/A	0.00% 0.02%	0.00% 0.01%
Seizure / Febrile convulsions	2	0	7	11
	0.02%	0.00%	0.05%	0.02%
	0.00% 0.04%	N/A N/A	0.01% 0.09%	0.01% 0.03%
Headache	26	6	119	337
	0.23%	0.17%	0.80%	0.60%
	0.15% 0.32%	0.06% 0.32%	0.66% 0.95%	0.53% 0.66%
Any neurological	31	6	133	357
	0.27%	0.17%	0.90%	0.63%
	0.18% 0.37%	0.06% 0.32%	0.75% 1.05%	0.57% 0.70%

Table 36 – Tabular summary of musculoskeletal adverse events (including specific conditions for the cohort by vaccination status, with confidence intervals

	AEI/IDE			
	AEI within 14-day post-vaccination		AEI/IDE at any time	
Musculoskeletal	*Vaccinated (Non-GSK)*	*Vaccinated (GSK)*	*Vaccinated*	*Non vaccinated*
Muscle aches / myalgia	54	32	357	543
	0.48%	0.93%	2.41%	0.96%
	0.35% 0.61%	0.61% 1.25%	2.17% 2.66%	0.88% 1.04%
Arthropathy	0	0	1	0
	0.00%	0.00%	0.01%	0.00%
	N/A N/A	N/A N/A	0.00% 0.02%	N/A N/A
Any musculoskeletal	54	32	357	543
	0.48%	0.93%	2.41%	0.96%
	0.35% 0.61%	0.61% 1.25%	2.17% 2.66%	0.88% 1.04%

Table 37 – Tabular summary of local symptoms adverse events (including specific conditions) for the cohort by vaccination status, with confidence intervals

	AEI/IDE			
	AEI within 14-day post-vaccination		AEI/IDE at any time	
Local symptoms	*Vaccinated (Non-GSK)*	*Vaccinated (GSK)*	*Vaccinated*	*Non vaccinated*
Local erythema	3	6	12	0
	0.03%	0.17%	0.08%	0.00%
	0.00% 0.06%	0.06% 0.32%	0.04% 0.13%	N/A N/A
Any local symptom	3	6	12	0
	0.03%	0.17%	0.08%	0.00%
	0.00% 0.06%	0.06% 0.32%	0.04% 0.13%	N/A N/A

Additionally, we report a break down of the rates of AEI/IDE in the cohort only for each broader category into age groups, risk group status, and surveillance method (Table 38 Table 47). We plan that any established process about AEIs should include a detailed breakdown that enables a vaccine manufacturer to have details of the basis on which any signal is based. Whilst this format can be developed to meet regulatory and manufacturers needs, the principal aim is to provide detailed data. There are limitations to the comparisons that can be made, especially between the vaccinated and non-vaccinated populations, as they are not matched on key characteristics. However, details on the characteristics of patients are presented to show the feasibility of extracting such data.

Table 38 – Tabular summary of all adverse events in the cohort by vaccination status (including age, risk group, and vaccine brand disaggregation), with confidence intervals

Any adverse event				
	AEI within 14-day post-vaccination		AEI/IDE at any time	
Age groups	***Vaccinated (Non-GSK)***	***Vaccinated (GSK)***	***Vaccinated***	***Non vaccinated***
<5yr	13	1	71	250
	3.94%	2.50%	19.19%	19.81%
	2.12% 6.06%	0.00% 7.50%	15.14% 23.24%	17.67% 22.03%
5-14yrs	19	1	113	356
	1.69%	1.96%	9.63%	5.75%
	0.98% 2.50%	0.00% 5.88%	8.01% 11.34%	5.19% 6.33%
15-64yrs	114	25	471	2029
	3.77%	3.20%	12.38%	4.81%
	3.11% 4.46%	2.05% 4.48%	11.35% 13.43%	4.61% 5.02%
65+ yrs	187	65	1106	304
	2.71%	2.54%	11.70%	4.36%
	2.34% 3.11%	1.95% 3.16%	11.06% 12.36%	3.88% 4.85%
	AEI within 14-day post-vaccination		**AEI/IDE at any time**	
Risk group	***Vaccinated (Non-GSK)***	***Vaccinated (GSK)***	***Vaccinated***	***Non vaccinated***
Any risk group	295	84	1562	1180
	3.05%	2.66%	12.17%	6.83%
	2.71% 3.40%	2.12% 3.23%	11.61% 12.73%	6.46% 7.21%
	AEI within 14-day post-vaccination		**AEI/IDE at any time**	
Surveillance method	***Vaccinated (Non-GSK)***	***Vaccinated (GSK)***	***Vaccinated***	***Non vaccinated***
Enhanced passive arm (n=3 GP practices)	31	92	500	0
	0.93%	2.68%	7.38%	N/A
	0.63% 1.26%	2.15% 3.23%	6.76% 8.01%	N/A N/A
EHR data mining arm (n=6 GP practices)	302	0	1261	2939
	3.76%	N/A	15.71%	5.19%
	3.35% 4.19%	N/A N/A	14.92% 16.51%	5.01% 5.38%

Table 39 – Tabular summary of respiratory adverse events in the cohort by vaccination status (including age, risk group, and vaccine brand disaggregation), with confidence intervals

Any Respiratory adverse event				
	AEI within 14-day post-vaccination		AEI/IDE at any time	
Age groups	*Vaccinated (Non-GSK)*	*Vaccinated (GSK)*	*Vaccinated*	*Non vaccinated*
<5yr	7	0	41	118
	2.12%	0.00%	11.08%	9.35%
	0.61% 3.94%	N/A N/A	8.11% 14.32%	7.77% 11.01%
5-14yrs	9	1	48	164
	0.80%	1.96%	4.09%	2.65%
	0.36% 1.34%	0.00% 5.88%	2.98% 5.29%	2.26% 3.05%
15-64yrs	30	5	152	556
	0.99%	0.64%	3.99%	1.32%
	0.66% 1.36%	0.13% 1.28%	3.39% 4.62%	1.21% 1.43%
65+ yrs	62	25	411	127
	0.90%	0.98%	4.35%	1.82%
	0.68% 1.13%	0.62% 1.37%	3.95% 4.76%	1.52% 2.14%
	AEI within 14-day post-vaccination		AEI/IDE at any time	
Risk group	*Vaccinated (Non-GSK)*	*Vaccinated (GSK)*	*Vaccinated*	*Non vaccinated*
Any risk group	92	29	574	421
	0.95%	0.92%	4.47%	2.44%
	0.76% 1.15%	0.60% 1.27%	4.12% 4.83%	2.21% 2.67%
	AEI within 14-day post-vaccination		AEI/IDE at any time	
Surveillance method	*Vaccinated (Non-GSK)*	*Vaccinated (GSK)*	*Vaccinated*	*Non vaccinated*
Enhanced passive arm (n=3 GP practices)	15	31	203	0
	0.45%	0.90%	3.00%	N/A
	0.24% 0.69%	0.61% 1.22%	2.60% 3.41%	N/A N/A
EHR data mining arm (n=6 GP practices)	93	0	449	965
	1.16%	N/A	5.60%	1.70%
	0.93% 1.40%	N/A N/A	5.10% 6.11%	1.60% 1.81%

Table 40 – Tabular summary of gastrointestinal adverse events in the cohort by vaccination status (including age, risk group, and vaccine brand disaggregation), with confidence intervals

Any Gastrointestinal adverse event								
	AEI within 14-day post-vaccination				AEI/IDE at any time			
Age groups	***Vaccinated (Non-GSK)***		***Vaccinated (GSK)***		***Vaccinated***		***Non vaccinated***	
<5yr	2		0		7		15	
	0.61%		0.00%		1.89%		1.19%	
	0.00%	1.52%	N/A	N/A	0.54%	3.51%	0.63%	1.82%
5-14yrs	0		0		8		23	
	0.00%		0.00%		0.68%		0.37%	
	N/A	N/A	N/A	N/A	0.26%	1.19%	0.23%	0.53%
15-64yrs	8		0		42		166	
	0.26%		0.00%		1.10%		0.39%	
	0.10%	0.46%	N/A	N/A	0.79%	1.45%	0.33%	0.46%
65+ yrs	14		2		144		28	
	0.20%		0.08%		1.52%		0.40%	
	0.10%	0.32%	0.00%	0.20%	1.28%	1.78%	0.26%	0.56%
	AEI within 14-day post-vaccination				**AEI/IDE at any time**			
Risk group	***Vaccinated (Non-GSK)***		***Vaccinated (GSK)***		***Vaccinated***		***Non vaccinated***	
Any risk group	22		2		185		86	
	0.23%		0.06%		1.44%		0.50%	
	0.13%	0.33%	0.00%	0.16%	1.24%	1.65%	0.39%	0.61%
	AEI within 14-day post-vaccination				**AEI/IDE at any time**			
Surveillance method	***Vaccinated (Non-GSK)***		***Vaccinated (GSK)***		***Vaccinated***		***Non vaccinated***	
Enhanced passive arm (n=3 GP practices)	4		2		53		0	
	0.12%		0.06%		0.78%		N/A	
	0.03%	0.24%	0.00%	0.15%	0.58%	1.00%	N/A	N/A
EHR data mining arm (n=6 GP practices)	20		0		148		232	
	0.25%		N/A		1.84%		0.41%	
	0.15%	0.36%	N/A	N/A	1.56%	2.14%	0.36%	0.46%

Table 41 – Tabular summary of fever/pyrexia adverse events in the cohort by vaccination status (including age, risk group, and vaccine brand disaggregation), with confidence intervals

Any Fever/Pyrexia event				
	AEI within 14-day post-vaccination		AEI/IDE at any time	
Age groups	***Vaccinated (Non-GSK)***	***Vaccinated (GSK)***	***Vaccinated***	***Non vaccinated***
<5yr	1	1	24	122
	0.30%	2.50%	6.49%	9.67%
	0.00% 0.91%	0.00% 7.50%	4.05% 9.19%	8.08% 11.33%
5-14yrs	4	1	43	113
	0.36%	1.96%	3.67%	1.83%
	0.09% 0.71%	0.00% 5.88%	2.64% 4.77%	1.50% 2.16%
15-64yrs	37	9	123	460
	1.22%	1.15%	3.23%	1.09%
	0.86% 1.62%	0.51% 1.92%	2.68% 3.81%	0.99% 1.19%
65+ yrs	45	12	248	44
	0.65%	0.47%	2.62%	0.63%
	0.46% 0.86%	0.23% 0.74%	2.31% 2.95%	0.46% 0.82%
	AEI within 14-day post-vaccination		**AEI/IDE at any time**	
Risk group	***Vaccinated (Non-GSK)***	***Vaccinated (GSK)***	***Vaccinated***	***Non vaccinated***
Any risk group	77	20	378	323
	0.80%	0.63%	2.94%	1.87%
	0.62% 0.98%	0.38% 0.92%	2.66% 3.24%	1.67% 2.07%
	AEI within 14-day post-vaccination		**AEI/IDE at any time**	
Surveillance method	***Vaccinated (Non-GSK)***	***Vaccinated (GSK)***	***Vaccinated***	***Non vaccinated***
Enhanced passive arm (n=3 GP practices)	7	23	98	0
	0.21%	0.67%	1.45%	N/A
	0.06% 0.39%	0.41% 0.96%	1.17% 1.74%	N/A N/A
EHR data mining arm (n=6 GP practices)	80	0	340	739
	1.00%	N/A	4.24%	1.31%
	0.79% 1.22%	N/A N/A	3.80% 4.69%	1.21% 1.40%

Table 42 – Tabular summary of sensitivity/anaphylaxis adverse events in the cohort by vaccination status (including age, risk group, and vaccine brand disaggregation), with confidence intervals

Any Sensitivity /Anaphylaxis event				
	AEI within 14-day post-vaccination		AEI/IDE at any time	
Age groups	*Vaccinated (Non-GSK)*	*Vaccinated (GSK)*	*Vaccinated*	*Non vaccinated*
<5yr	1	0	1	2
	0.30%	0.00%	0.27%	0.16%
	0.00% 0.91%	N/A N/A	0.00% 0.81%	0.00% 0.40%
5-14yrs	2	0	5	5
	0.18%	0.00%	0.43%	0.08%
	0.00% 0.45%	N/A N/A	0.09% 0.85%	0.02% 0.16%
15-64yrs	0	0	4	25
	0.00%	0.00%	0.11%	0.06%
	N/A N/A	N/A N/A	0.03% 0.21%	0.04% 0.08%
65+ yrs	2	0	6	5
	0.03%	0.00%	0.06%	0.07%
	0.00% 0.07%	N/A N/A	0.02% 0.12%	0.01% 0.14%
	AEI within 14-day post-vaccination		AEI/IDE at any time	
Risk group	*Vaccinated (Non-GSK)*	*Vaccinated (GSK)*	*Vaccinated*	*Non vaccinated*
Any risk group	3	0	9	14
	0.03%	0.00%	0.07%	0.08%
	0.00% 0.07%	N/A N/A	0.03% 0.12%	0.04% 0.13%
	AEI within 14-day post-vaccination		AEI/IDE at any time	
Surveillance method	*Vaccinated (Non-GSK)*	*Vaccinated (GSK)*	*Vaccinated*	*Non vaccinated*
Enhanced passive arm (n=3 GP practices)	1	0	9	0
	0.03%	0.00%	0.13%	N/A
	0.00% 0.09%	N/A N/A	0.06% 0.22%	N/A N/A
EHR data mining arm (n=6 GP practices)	4	0	7	37
	0.05%	N/A	0.09%	0.07%
	0.01% 0.10%	N/A N/A	0.02% 0.16%	0.05% 0.09%

Table 43 – Tabular summary of rash adverse events in the cohort by vaccination status (including age, risk group, and vaccine brand disaggregation), with confidence intervals

Any Rash event				
	AEI within 14-day post-vaccination		AEI/IDE at any time	
Age groups	***Vaccinated (Non-GSK)***	***Vaccinated (GSK)***	***Vaccinated***	***Non vaccinated***
<5yr	3	0	9	42
	0.91%	0.00%	2.43%	3.33%
	0.00% 2.12%	N/A N/A	1.08% 4.05%	2.38% 4.36%
5-14yrs	3	0	16	49
	0.27%	0.00%	1.36%	0.79%
	0.00% 0.62%	N/A N/A	0.77% 2.05%	0.58% 1.02%
15-64yrs	6	1	42	135
	0.20%	0.13%	1.10%	0.32%
	0.07% 0.36%	0.00% 0.38%	0.79% 1.45%	0.27% 0.37%
65+ yrs	12	6	83	24
	0.17%	0.23%	0.88%	0.34%
	0.09% 0.28%	0.08% 0.43%	0.70% 1.07%	0.22% 0.49%
	AEI within 14-day post-vaccination		**AEI/IDE at any time**	
Risk group	***Vaccinated (Non-GSK)***	***Vaccinated (GSK)***	***Vaccinated***	***Non vaccinated***
Any risk group	19	7	127	113
	0.20%	0.22%	0.99%	0.65%
	0.11% 0.29%	0.06% 0.41%	0.83% 1.16%	0.54% 0.78%
	AEI within 14-day post-vaccination		**AEI/IDE at any time**	
Surveillance method	***Vaccinated (Non-GSK)***	***Vaccinated (GSK)***	***Vaccinated***	***Non vaccinated***
Enhanced passive arm (n=3 GP practices)	0	7	35	0
	0.00%	0.20%	0.52%	N/A
	N/A N/A	0.06% 0.38%	0.35% 0.69%	N/A N/A
EHR data mining arm (n=6 GP practices)	24	0	115	250
	0.30%	N/A	1.43%	0.44%
	0.19% 0.42%	N/A N/A	1.18% 1.69%	0.39% 0.50%

Table 44 – Tabular summary of general adverse events in the cohort by vaccination status (including age, risk group, and vaccine brand disaggregation), with confidence intervals

Any General event								
	AEI within 14-day post-vaccination				AEI/IDE at any time			
Age groups	***Vaccinated (Non-GSK)***		***Vaccinated (GSK)***		***Vaccinated***		***Non vaccinated***	
<5yr	1		0		6		9	
	0.30%		0.00%		1.62%		0.71%	
	0.00%	0.91%	N/A	N/A	0.54%	2.97%	0.32%	1.19%
5-14yrs	3		0		6		10	
	0.27%		0.00%		0.51%		0.16%	
	0.00%	0.62%	N/A	N/A	0.17%	0.94%	0.06%	0.27%
15-64yrs	9		0		24		146	
	0.30%		0.00%		0.63%		0.35%	
	0.13%	0.50%	N/A	N/A	0.39%	0.89%	0.29%	0.40%
65+ yrs	10		8		90		22	
	0.15%		0.31%		0.95%		0.32%	
	0.06%	0.25%	0.12%	0.55%	0.76%	1.15%	0.19%	0.46%
	AEI within 14-day post-vaccination				**AEI/IDE at any time**			
Risk group	***Vaccinated (Non-GSK)***		***Vaccinated (GSK)***		***Vaccinated***		***Non vaccinated***	
Any risk group	19		8		114		77	
	0.20%		0.25%		0.89%		0.45%	
	0.11%	0.29%	0.10%	0.44%	0.73%	1.05%	0.35%	0.55%
	AEI within 14-day post-vaccination				**AEI/IDE at any time**			
Surveillance method	***Vaccinated (Non-GSK)***		***Vaccinated (GSK)***		***Vaccinated***		***Non vaccinated***	
Enhanced passive arm (n=3 GP practices)	6		8		54		0	
	0.18%		0.23%		0.80%		N/A	
	0.06%	0.33%	0.09%	0.41%	0.59%	1.02%	N/A	N/A
EHR data mining arm (n=6 GP practices)	17		0		72		187	
	0.21%		N/A		0.90%		0.33%	
	0.11%	0.32%	N/A	N/A	0.70%	1.11%	0.28%	0.38%

Table 45 – Tabular summary of neurological adverse events in the cohort by vaccination status (including age, risk group, and vaccine brand disaggregation), with confidence intervals

Any Neurological event								
	AEI within 14-day post-vaccination				AEI/IDE at any time			
Age groups	***Vaccinated (Non-GSK)***		***Vaccinated (GSK)***		***Vaccinated***		***Non vaccinated***	
<5yr	0		0		1		3	
	0.00%		0.00%		0.27%		0.24%	
	N/A	N/A	N/A	N/A	0.00%	0.81%	0.00%	0.55%
5-14yrs	1		0		7		18	
	0.09%		0.00%		0.60%		0.29%	
	0.00%	0.27%	N/A	N/A	0.17%	1.11%	0.16%	0.44%
15-64yrs	14		0		59		315	
	0.46%		0.00%		1.55%		0.75%	
	0.23%	0.73%	N/A	N/A	1.18%	1.94%	0.67%	0.83%
65+ yrs	16		6		66		21	
	0.23%		0.23%		0.70%		0.30%	
	0.13%	0.35%	0.08%	0.43%	0.54%	0.87%	0.19%	0.43%
	AEI within 14-day post-vaccination				**AEI/IDE at any time**			
Risk group	***Vaccinated (Non-GSK)***		***Vaccinated (GSK)***		***Vaccinated***		***Non vaccinated***	
Any risk group	29		6		117		124	
	0.30%		0.19%		0.91%		0.72%	
	0.20%	0.41%	0.06%	0.35%	0.75%	1.08%	0.60%	0.85%
	AEI within 14-day post-vaccination				**AEI/IDE at any time**			
Surveillance method	***Vaccinated (Non-GSK)***		***Vaccinated (GSK)***		***Vaccinated***		***Non vaccinated***	
Enhanced passive arm (n=3 GP practices)	2		6		37		0	
	0.06%		0.17%		0.55%		N/A	
	0.00%	0.15%	0.06%	0.32%	0.38%	0.72%	N/A	N/A
EHR data mining arm (n=6 GP practices)	29		0		96		357	
	0.36%		N/A		1.20%		0.63%	
	0.24%	0.50%	N/A	N/A	0.96%	1.45%	0.57%	0.70%

Table 46 – Tabular summary of musculoskeletal adverse events in the cohort by vaccination status (including age, risk group, and vaccine brand disaggregation), with confidence intervals

Any Musculoskeletal event								
	AEI within 14-day post-vaccination				AEI/IDE at any time			
Age groups	*Vaccinated (Non-GSK)*		*Vaccinated (GSK)*		*Vaccinated*		*Non vaccinated*	
<5yr	0		0		0		2	
	0.00%		0.00%		0.00%		0.16%	
	N/A	N/A	N/A	N/A	N/A	N/A	0.00%	0.40%
5-14yrs	0		0		2		29	
	0.00%		0.00%		0.17%		0.47%	
	N/A	N/A	N/A	N/A	0.00%	0.43%	0.31%	0.65%
15-64yrs	21		11		104		435	
	0.69%		1.41%		2.73%		1.03%	
	0.43%	0.99%	0.64%	2.30%	2.23%	3.26%	0.94%	1.13%
65+ yrs	33		21		251		77	
	0.48%		0.82%		2.66%		1.10%	
	0.32%	0.65%	0.51%	1.17%	2.34%	2.98%	0.86%	1.36%
	AEI within 14-day post-vaccination				AEI/IDE at any time			
Risk group	*Vaccinated (Non-GSK)*		*Vaccinated (GSK)*		*Vaccinated*		*Non vaccinated*	
Any risk group	54		29		337		199	
	0.56%		0.92%		2.62%		1.15%	
	0.41%	0.71%	0.60%	1.27%	2.35%	2.91%	1.00%	1.31%
	AEI within 14-day post-vaccination				AEI/IDE at any time			
Surveillance method	*Vaccinated (Non-GSK)*		*Vaccinated (GSK)*		*Vaccinated*		*Non vaccinated*	
Enhanced passive arm (n=3 GP practices)	0		32		95		0	
	0.00%		0.93%		1.40%		N/A	
	N/A	N/A	0.61%	1.25%	1.14%	1.68%	N/A	N/A
EHR data mining arm (n=6 GP practices)	54		0		262		543	
	0.67%		N/A		3.26%		0.96%	
	0.50%	0.86%	N/A	N/A	2.88%	3.66%	0.88%	1.04%

Table 47 – Tabular summary of local adverse events in the cohort by vaccination status (including age, risk group, and vaccine brand disaggregation), with confidence intervals

Any Local event				
	AEI within 14-day post-vaccination		AEI/IDE at any time	
Age groups	*Vaccinated (Non-GSK)*	*Vaccinated (GSK)*	*Vaccinated*	*Non vaccinated*
<5yr	0	0	0	0
	0.00%	0.00%	0.00%	0.00%
	N/A N/A	N/A N/A	N/A N/A	N/A N/A
5-14yrs	0	0	0	0
	0.00%	0.00%	0.00%	0.00%
	N/A N/A	N/A N/A	N/A N/A	N/A N/A
15-64yrs	2	1	5	0
	0.07%	0.13%	0.13%	0.00%
	0.00% 0.17%	0.00% 0.38%	0.03% 0.26%	N/A N/A
65+ yrs	1	5	7	0
	0.01%	0.20%	0.07%	0.00%
	0.00% 0.04%	0.04% 0.39%	0.02% 0.14%	N/A N/A
	AEI within 14-day post-vaccination		AEI/IDE at any time	
Risk group	*Vaccinated (Non-GSK)*	*Vaccinated (GSK)*	*Vaccinated*	*Non vaccinated*
Any risk group	3	6	12	0
	0.03%	0.19%	0.09%	0.00%
	0.00% 0.07%	0.06% 0.35%	0.05% 0.15%	N/A N/A
	AEI within 14-day post-vaccination		AEI/IDE at any time	
Surveillance method	*Vaccinated (Non-GSK)*	*Vaccinated (GSK)*	*Vaccinated*	*Non vaccinated*
Enhanced passive arm (n=3 GP practices)	1	6	10	0
	0.03%	0.17%	0.15%	N/A
	0.00% 0.09%	0.06% 0.32%	0.06% 0.25%	N/A N/A
EHR data mining arm (n=6 GP practices)	2	0	2	0
	0.02%	N/A	0.02%	0.00%
	0.00% 0.06%	N/A N/A	0.00% 0.06%	N/A N/A

The three enhanced passive surveillance practices handed out yellow cards to 61% (4150/6776) of the vaccinated population; 2% (82/4150) of these cards were returned, representing 1.2% (82/6776) of the vaccinated population. The rates of distribution were different but the response rates were similar in the GSK and non GSK practices (Table 48).

In the one enhanced passive surveillance practice with a non-GSK vaccine, the AEIs recorded in the data (from the cohort) are lower than the number of yellow cards returned; this shows a potential limitation of the method, in that data completeness may be limited by practice staff failing to record the data on returned yellow cards.

The rate of return of yellow cards is much lower than the detection rate of AEIs in the EHR data mining method. In the post vaccination 14-day window, the rates of identification of AIEs was 3.0% (non-GSK) and 2.6% (GSK) from the repeated cross-sectional data collection, with 2.9% (non-GSK) and 2.7% (GSK) as the rates in the retrospective cohort study. In terms of overall rate, the yellow card (enhanced passive surveillance) system found far fewer cases (1.2%).

***Table 48*– Summary of enhanced passive surveillance arm: rate of delivery and return of Yellow Cards – N.B. the 2% return rate is of the cards handed out**

GSK Vaccine	Registered population	Vaccinated population		Yellow cards handed out		Yellow cards returned		Adverse Events recorded at any time		Adverse Events recorded (14 days post-vaccination)	
		Count	%	Count	%	Count	%	Count	%	Count	%
N	11997	3342	28%	2400	72%	48	2%	130	4%	31	1%
Y	13891	3434	25%	1750	51%	34	2%	370	11%	92	3%

8.3. Severity

8.3.1. Hospitalisation

We are not presenting data from the weekly cross-sectional surveillance. Although this could be included, hospital data/diagnoses often take 10-20 days to be recorded in the GP record and it can be up to 42 days. Based on the cohort study, for all of the recorded AEIs within 14-days post-vaccination (n=425), only 15 vaccinated patients were hospitalised within 10 days (before or after) of the AEI being recorded in the EHR. 2.2% (n=2; 95%CI 0.0%-5.4%) of people with a GSK vaccine were admitted to hospital concurrent with an AEI in the 14 days following vaccination; compared with 3.9% (n=13; 95%CI 2.1%-6.0%) in the non-GSK vaccinated group.

Figure 15 shows the rates of hospitalisation for vaccinated patients only concurrent with an AEI happening 14-days post-vaccination, by broad category of AEIs, and comparing vaccine brands. The rate is determined as patients with a concurrent hospitalisation as a proportion of patients with an AEI, reported for each category. Therefore, while hospitalisations concurrent with neurological and rash-related AEIs are relatively low (4 and 1, respectively), they represent a high proportion of AEIs reported in those categories.

Figure 16 shows a similar structure of rates, but for hospitalisations concurrent with AEIs happening at any point over the study period, and comparing vaccinated and non-vaccinated patients. Over the whole 15 week observation period admissions of vaccinated people to hospital concurrent with an AEI/IDE were 2.5% (n=44, 95% CI 1.8%-3.2%) across all vaccinated compared with 1.0% (n=30, 95%CI 0.7%-1.4%) in the non-vaccinated group. Confidence intervals in both figures are shown as error bars.

The most common AEI related to a hospitalisation was fever (5 cases in the 14-day post-vaccination period, and 31 at any time during the study period). Given that fever is a common symptom within a number of conditions requiring emergency care, it may not be possible to determine the direct cause of the hospitalisation, without investigating each individual patient's EHR around the relevant dates. Table 49 shows a disaggregation of patients with a concurrent hospitalisation event by age group, risk group, and surveillance method. As expected, the majority of the hospitalisations concurrent with AEIs happened for people within the high risk group (14 cases for AEIs in the 14-day post-vaccination window, and 63 cases for AEIs at any point during the study period).

Figure 15– Hospitalisation concurrent with AEI for vaccinated patients (14 days post-vaccination) by category and vaccine brand

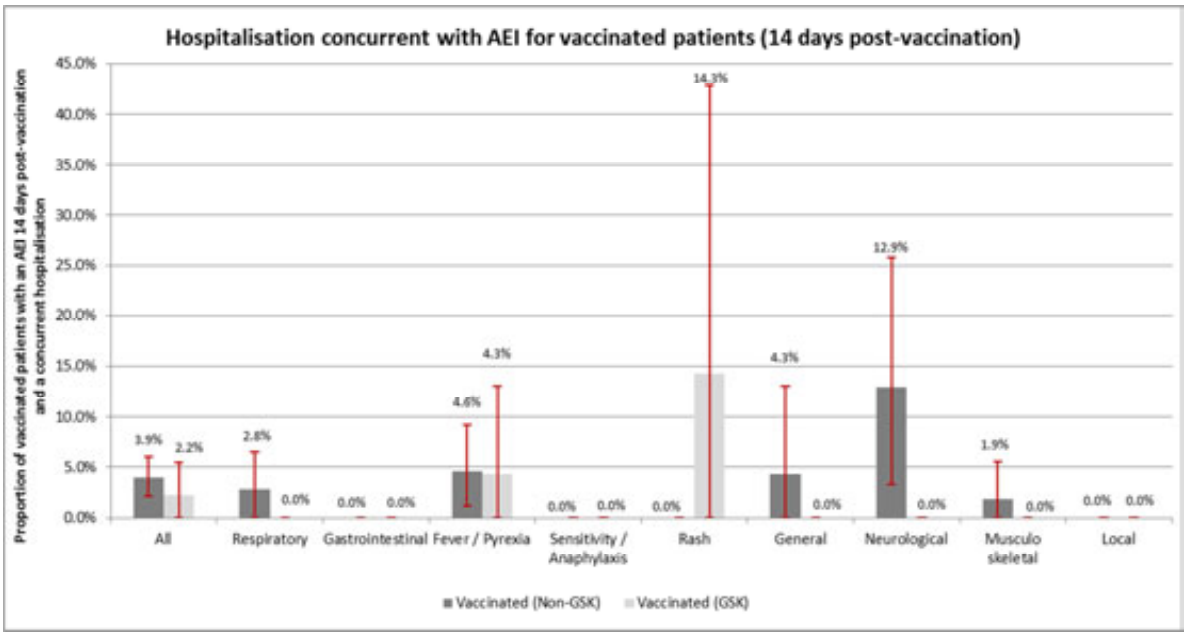


Figure 16 – Hospitalisation concurrent with AEI (any time during study period) by category and vaccination status

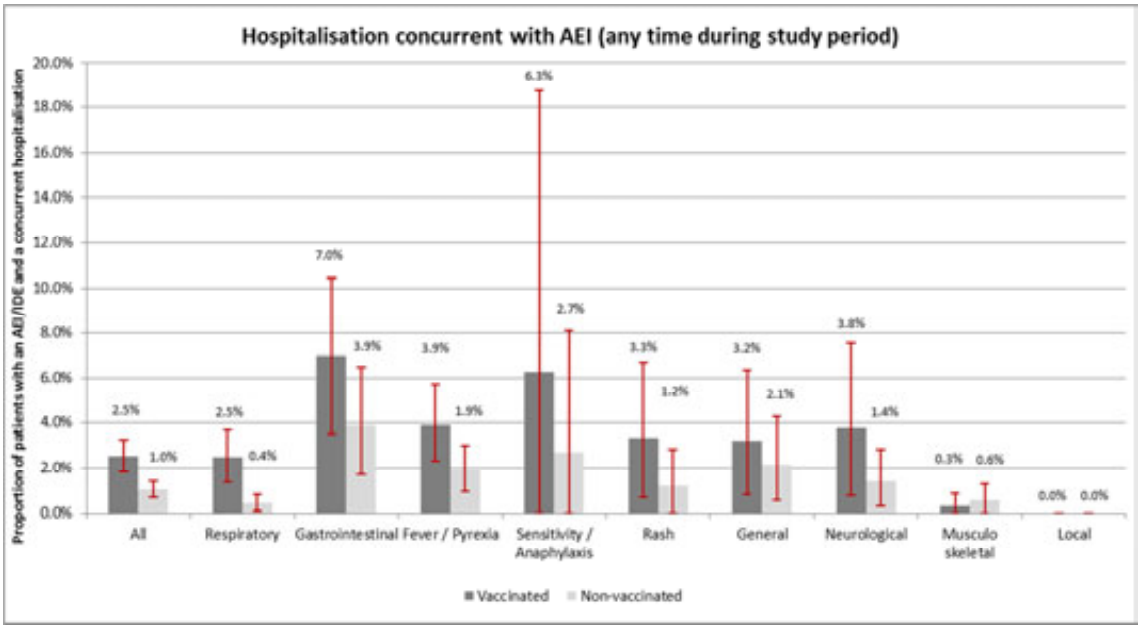


Table 49 – **Tabular summary of patients with a hospitalisation concurrent with AEI/IDE**

Concurrent hospitalisation with any AEI								
	AEI within 14-day post-vaccination				AEI/IDE at any time			
Any AEI	*Vaccinated (Non-GSK)*		*Vaccinated (GSK)*		*Vaccinated*		*Non vaccinated*	
Concurrent hospitalisation with any AEI	13		2		44		30	
	3.90%		2.17%		2.50%		1.02%	
	2.10%	6.01%	0.00%	5.43%	1.82%	3.24%	0.68%	1.40%
	AEI within 14-day post-vaccination				AEI/IDE at any time			
Age groups	*Vaccinated (Non-GSK)*		*Vaccinated (GSK)*		*Vaccinated*		*Non vaccinated*	
<5yr	0		0		2		2	
	0.00%		0.00%		2.82%		0.80%	
	N/A	N/A	N/A	N/A	0.00%	7.04%	0.00%	2.00%
5-14yrs	0		0		0		2	
	0.00%		0.00%		0.00%		0.56%	
	N/A	N/A	N/A	N/A	N/A	N/A	0.00%	1.40%
15-64yrs	2		1		8		17	
	1.75%		4.00%		1.70%		0.84%	
	0.00%	4.39%	0.00%	12.00%	0.64%	2.97%	0.44%	1.23%
65+ yrs	11		1		34		9	
	5.88%		1.54%		3.07%		2.96%	
	2.67%	9.63%	0.00%	4.62%	2.08%	4.16%	1.32%	4.93%
	AEI within 14-day post-vaccination				AEI/IDE at any time			
Risk group	*Vaccinated (Non-GSK)*		*Vaccinated (GSK)*		*Vaccinated*		*Non vaccinated*	
Any risk group	13		1		43		20	
	4.41%		1.19%		2.75%		1.69%	
	2.37%	6.78%	0.00%	3.57%	1.98%	3.59%	1.02%	2.46%
	AEI within 14-day post-vaccination				AEI/IDE at any time			
Surveillance method	*Vaccinated (Non-GSK)*		*Vaccinated (GSK)*		*Vaccinated*		*Non vaccinated*	
Enhanced passive arm (n=3 GP practices)	0		2		7		0	
	0.00%		2.17%		1.40%		N/A	
	N/A	N/A	0.00%	5.43%	0.40%	2.60%	N/A	N/A
EHR data mining arm (n=6 GP practices)	13		0		37		30	
	4.30%		N/A		2.93%		1.02%	
	2.32%	6.62%	N/A	N/A	2.06%	3.89%	0.68%	1.40%

8.3.2. Fever

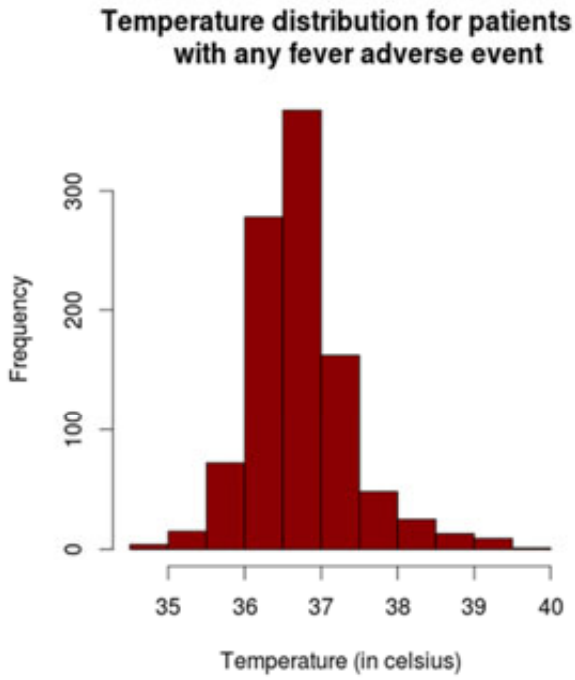
Fever, temperature symptoms, and pyrexia can all be coded by the GP into the clinical record. We find these are used as synonyms, and so can be aggregated for analysis (n=1177 occurring at any time during the study period, n=110 14-days' post-vaccination in the cohort data). A coded entry of this sort can mean that the clinician is recording fever or temperature symptoms as

part of the history (n=138 at any time, 23 post-vaccination), or as an examination finding with an associated numeric (n=1055 at any time, 89 post-vaccination); though sometimes the numeric value is one provided by the patient. Occasionally both are recorded in a consultation (n=16 at any time, 2 post-vaccination).

We analysed all the temperatures recorded against patients with coded fever at any time during the study period (n=1177). The mean temperature was 36.78 degrees Celsius (s.d. 0.66). The method of measuring the fever (orally, rectally, axillary, etc.) is not always recorded, and it can have an impact on the relevant temperature ranges. Equally, there is no record of the time of day or whether the patient has taken an antipyretic; all of these can have an impact on the temperature.

Similar proportions of people had their temperature recorded numerically in the 14 days post-vaccination; 0.50% (95%CI 0.26%-0.73%) in those vaccinated with the GSK brand and 0.63% (95%CI 0.49%-0.78%) in those vaccinated with other brands of influenza vaccine. Background rates across the whole observation period were 2.66% (95%CI 2.40%-2.92%) for those vaccinated and 1.17% (95%CI 1.08%-1.26%) for subjects who were not.

Figure 17 **– Temperature distribution for patients coded/reported with fever (n=1144)**



8.4. Statistical analysis

8.4.1. Crude odds ratios

As in previous sections, our analysis compares two sets of groups. Firstly, the primary comparison of GSK and non-GSK brands of influenza vaccines; the comparison is made of AEIs being reported in the 14 days post-vaccination window for vaccinated patients only. The second

comparison looks at the rates of AEIs in all influenza vaccinated patients compared with rates of the same conditions (IDEs) among the non-vaccinated. The second comparison is for AEIs reported at any point over the whole observation period (week 35 to 49). The groups in the second comparison are not matched and are included to provide insight into the epidemiology of conditions (AEIs/IDEs) that may have shown signals that may not be related to vaccine exposure.

For all categories, the crude odds ratios provided a basis for comparing the two different influenza vaccines categories (GSK-vaccine, and non GSK vaccine) being associated with any of the groups of AEIs in the 14 day post vaccination observation period (Table 50), demonstrating the feasibility of conducting such an analysis. Because of heterogeneity between the arms of the study, we do not claim this as a robust demonstration of differences. However, a definitive study would be capable of reporting results like these.

Table 50– Tabular summary of crude odds ratios, by adverse event category (vaccination status with non-vaccinated as a reference category, and surveillance method with enhanced passive surveillance as a reference category)

Population	Vaccinated patients				All registered patients			
Exposure	Vaccine brand (GSK or non-GSK - Reference: non-GSK)				Vaccination status (Vaccinated or not vaccinated - Reference: not vaccinated)			
Outcome	AEIs within 14 days post vaccination				AEIs/IDEs at any time			
	OR	LCI	UCI	p-value	OR	LCI	UCI	p-value
All	0.91	0.72	1.15	0.44	2.47	2.32	2.62	0.00
Respiratory	0.95	0.63	1.40	0.80	2.66	2.40	2.94	0.00
Gastrointestinal	0.28	0.04	0.93	0.08	3.35	2.77	4.04	0.00
Fever / Pyrexia	0.87	0.54	1.36	0.57	2.31	2.04	2.60	0.00
Sensitivity / Anaphylaxis	N/A	N/A	N/A	N/A	1.65	0.90	2.92	0.09
Rash	0.97	0.38	2.13	0.93	2.31	1.88	2.82	0.00
General	1.15	0.48	2.47	0.73	2.59	2.06	3.24	0.00
Neurological	0.64	0.24	1.43	0.32	1.43	1.17	1.74	0.00
Musculoskeletal	1.97	1.26	3.04	0.00	2.55	2.23	2.92	0.00
Local	6.64	1.75	31.46	0.01	N/A	N/A	N/A	N/A

Crude odds ratios of an AEI were no different for GSK and non-GSK brands of vaccine in the 14-day period post-vaccination; OR 0.91 (95%CI 0.72%-1.15%; p=0.44). The only significant differences observed were a higher probability of musculoskeletal (OR 1.97, 95%CI 1.26-3.04, p<0.00) and local AEIs (OR 6.64, 95%CI 1.75-31.46, p=0.01) for those vaccinated with the GSK brand, compared to other brands. However, the latter should be treated with caution because GSK vaccine was only in the enhanced passive surveillance (yellow card) arm and this AEI was reported more in this arm.

All odds ratios were significant in the second group comparison (vaccinated and non-vaccinated, for AEIs occurring at any point during the study period), with the exception of AEIs

within the sensitivity/anaphylaxis category. The odds ratios show that vaccinated patients have a higher probability of developing an AEI compared with non-vaccinated subjects, across all categories of AEIs. It is not possible to determine odds ratios for local and injection site adverse events, since non-vaccinated patients would not develop these (e.g. erythema at the site of injection).

Whilst any patient can produce a local rash or redness of the skin due to a range of causes, this type of event has been classified under the rash broad category; an injection site adverse event (under the local broad category) can only happen if the individual underwent an injection. Similarly, as there were no sensitivity/anaphylaxis AEIs for patients receiving the GSK vaccine, the odds ratio was only relevant in comparing non-vaccinated patients and patients vaccinated with a non-GSK vaccine.

8.4.2. Multivariate Logistic regression

The multivariate logistic regression, as all of the analysis thus far, makes two comparisons: AEIs in the 14 days post vaccination for vaccinated patients only, by GSK and non-GSK vaccine brand; and all AEIs occurring over the whole observation period, by vaccinated and not vaccinated. We conducted a multivariate logistic regression to determine the impact of a number of variables on the probability of developing an AEI (Table 51), including vaccination status, age, gender, ethnicity, IMD score, risk group status, surveillance method, and concomitant vaccines.

The comparison between GSK vs. non-GSK in the 14-day post-vaccination window showed that the OR of reporting an AEI for GSK vaccinated people was 2.91 (95%CI 1.76-4.90; $p<0.001$) compared with non-GSK, when controlling for a number of variables. Method of surveillance showed EHR data mining to have an OR of recording an AEI of 4.07 (95%CI 2.51-6.69; $p<0.001$). Male gender is associated with lower levels of AEI recording; the OR is 0.68 (95%CI 0.55-0.83; $p<0.001$.

The comparison between vaccinated and non-vaccinated for the whole of the study period, showed that the OR of reporting an AEI among those vaccinated was 2.07 (95%CI 1.91-2.26; $p<0.001$) compared with non-vaccinated. People in a high risk group were more likely to present with an AEI/IDE 1.72 (95%CI 1.60-1.86; $p<0.001$). The method of surveillance showed EHR data mining to have an OR of recording an AEI/IDE of 1.54 (95%CI 1.38-173; $p<0.001$). Male gender is associated with lower levels of AE recording; the OR is 0.71 (95%CI 0.67-0.75; $p<0.001$.

It is likely that practice factors and other impacts such as propensity to consult may account for why these factors impact on the OR of reporting AEIs/IDEs. We present detailed tables for each type of AEI (Table 31 to 40). This should allow a vaccine manufacturer or other interested party to have more detailed information about the basis of any reported signal. The format for these should be defined ahead of any future study.

As stated previously, the surveillance method is a strong predictor, but may also be influenced by potential bias in the data collection method. The results for the enhanced passive surveillance is based on three practices, and practice factors may have been important. The non-GSK enhanced passive surveillance practice recorded less AEI than the number of yellow cards it received. This suggests under recording and may have distorted results.

We also had concerns that the focus of the enhanced passive surveillance practices was on their first use of the yellow card scheme. Much of the study team's interaction with those practices was over the distribution, collection, and coding of the yellow cards; whilst, by way of contrast, the EHR data mining practices focus was on the list of codes for AEIs/IDEs. It is possible that this led to greater coding of AEIs/IDEs in the EHR data mining practice.

Table 51– Tabular summary of multivariate logistic regression results for all adverse events

Any adverse event								
Population	Vaccinated patients				All registered patients			
Outcome	AEIs within 14 days post vaccination				AEIs/IDEs at any time			
	OR	LCI	UCI	p-value	OR	LCI	UCI	p-value
GSK vaccine (Reference: non-GSK vaccine)	2.91	1.76	4.90	0.00	N/A	N/A	N/A	N/A
Vaccinated (Reference: Non-vaccinated)	N/A	N/A	N/A	N/A	2.07	1.90	2.26	0.00
Age	1.00	0.99	1.00	0.07	0.99	0.99	0.99	0.00
Gender: Male (Reference: Female)	0.68	0.55	0.83	0.00	0.71	0.67	0.75	0.00
Ethnicity: Asian (Reference: White)	0.56	0.17	1.33	0.26	0.70	0.56	0.87	0.00
Ethnicity: Black (Reference: White)	0.00	N/A	N/A	0.98	0.63	0.38	0.99	0.06
Ethnicity: Mixed (Reference: White)	0.00	0.00	34.23	0.97	0.78	0.50	1.16	0.24
Ethnicity: Other (Reference: White)	0.00	N/A	N/A	0.98	0.62	0.34	1.02	0.08
Ethnicity: Unknown (Reference: White)	0.94	0.67	1.29	0.73	0.37	0.34	0.40	0.00
IMD Score	1.00	0.98	1.00	0.34	1.00	1.00	1.00	0.58
Any high risk group	1.39	0.98	2.02	0.07	1.72	1.60	1.86	0.00
Surveillance method: EHR data mining (Reference: Enhanced passive)	4.07	2.51	6.69	0.00	1.54	1.38	1.73	0.00
Any concomitant vaccine	0.87	0.34	1.82	0.74	1.07	0.70	1.58	0.74

Table 52– Tabular summary of multivariate logistic regression results for respiratory adverse events

Respiratory								
Population	Vaccinated patients				All registered patients			
Outcome	AEIs within 14 days post vaccination				AEIs/IDEs at any time			
	OR	LCI	UCI	p-value	OR	LCI	UCI	p-value
GSK vaccine (Reference: non-GSK vaccine)	2.58	1.20	5.61	0.01	N/A	N/A	N/A	N/A
Vaccinated (Reference: Non-vaccinated)	N/A	N/A	N/A	N/A	2.18	1.90	2.50	0.00
Age	1.00	0.99	1.00	0.39	0.99	0.99	0.99	0.00
Gender: Male (Reference: Female)	0.75	0.53	1.07	0.12	0.89	0.80	0.99	0.02
Ethnicity: Asian (Reference: White)	0.00	0.00	2.05	0.98	0.51	0.32	0.76	0.00
Ethnicity: Black (Reference: White)	0.00	N/A	N/A	0.99	0.56	0.20	1.23	0.21
Ethnicity: Mixed (Reference: White)	0.00	0.00	N/A	0.99	0.86	0.41	1.57	0.65
Ethnicity: Other (Reference: White)	0.00	N/A	N/A	0.99	0.57	0.17	1.34	0.26
Ethnicity: Unknown (Reference: White)	1.27	0.74	2.07	0.36	0.46	0.41	0.52	0.00
IMD Score	1.00	0.98	1.01	0.79	0.99	0.99	1.00	0.04
Any high risk group	1.12	0.63	2.09	0.70	2.02	1.78	2.28	0.00
Surveillance method: EHR data mining (Reference: Enhanced passive)	3.21	1.56	6.71	0.00	1.34	1.12	1.60	0.00
Any concomitant vaccine	0.97	0.16	3.11	0.96	1.23	0.64	2.14	0.50

Table 53 – Tabular summary of multivariate logistic regression results for gastrointestinal adverse events

Gastrointestinal								
Population Outcome	Vaccinated patients AEIs within 14 days post vaccination				All registered patients AEIs/IDEs at any time			
	OR	LCI	UCI	p-value	OR	LCI	UCI	p-value
GSK vaccine (Reference: non-GSK vaccine)	0.41	0.04	3.02	0.42	N/A	N/A	N/A	N/A
Vaccinated (Reference: Non-vaccinated)	N/A	N/A	N/A	N/A	2.75	2.11	3.56	0.00
Age	1.00	0.98	1.02	0.91	1.00	0.99	1.00	0.63
Gender: Male (Reference: Female)	0.88	0.39	1.90	0.74	0.79	0.65	0.96	0.02
Ethnicity: Asian (Reference: White)	2.62	0.14	13.06	0.35	0.64	0.27	1.27	0.25
Ethnicity: Black (Reference: White)	0.00	N/A	N/A	0.99	1.33	0.33	3.53	0.62
Ethnicity: Mixed (Reference: White)	0.00	N/A	N/A	0.99	0.80	0.13	2.51	0.75
Ethnicity: Other (Reference: White)	0.00	N/A	N/A	0.99	0.58	0.03	2.59	0.59
Ethnicity: Unknown (Reference: White)	0.85	0.13	2.99	0.83	0.39	0.30	0.49	0.00
IMD Score	1.02	0.98	1.05	0.35	1.00	0.99	1.01	0.59
Any high risk group	1.79	0.42	12.44	0.48	1.41	1.09	1.81	0.01
Surveillance method: EHR data mining (Reference: Enhanced passive)	1.75	0.24	9.27	0.52	1.70	1.23	2.39	0.00
Any concomitant vaccine	2.16	0.12	10.62	0.46	1.22	0.37	2.93	0.70

Table 54 – Tabular summary of multivariate logistic regression results for fever/pyrexia adverse events

Fever/Pyrexia								
Population	Vaccinated patients				All registered patients			
Outcome	AEIs within 14 days post vaccination				AEIs/IDEs at any time			
	OR	LCI	UCI	p-value	OR	LCI	UCI	p-value
GSK vaccine (Reference: non-GSK vaccine)	1.30	0.36	4.29	0.67	N/A	N/A	N/A	N/A
Vaccinated (Reference: Non-vaccinated)	N/A	N/A	N/A	N/A	2.14	1.83	2.50	0.00
Age	0.99	0.98	1.00	0.01	0.98	0.98	0.98	0.00
Gender: Male (Reference: Female)	0.62	0.41	0.92	0.02	0.71	0.63	0.80	0.00
Ethnicity: Asian (Reference: White)	1.45	0.35	3.94	0.53	0.84	0.57	1.19	0.34
Ethnicity: Black (Reference: White)	0.00	N/A	N/A	0.99	0.87	0.37	1.72	0.72
Ethnicity: Mixed (Reference: White)	0.00	0.00	N/A	0.99	0.90	0.43	1.66	0.76
Ethnicity: Other (Reference: White)	0.00	N/A	N/A	0.99	0.63	0.19	1.49	0.36
Ethnicity: Unknown (Reference: White)	0.37	0.13	0.82	0.03	0.27	0.23	0.31	0.00
IMD Score	1.00	0.98	1.01	0.69	1.01	1.00	1.01	0.03
Any high risk group	1.48	0.79	2.98	0.24	2.20	1.91	2.53	0.00
Surveillance method: EHR data mining (Reference: Enhanced passive)	1.78	0.52	5.66	0.33	1.61	1.28	2.05	0.00
Any concomitant vaccine	0.00	0.00	9.01	0.98	1.12	0.47	2.24	0.77

Table 55 – Tabular summary of multivariate logistic regression results for sensitivity/anaphylaxis adverse events

Sensitivity/Anaphylaxis								
Population	Vaccinated patients				All registered patients			
Outcome	AEIs within 14 days post vaccination				AEIs/IDEs at any time			
	OR	LCI	UCI	p-value	OR	LCI	UCI	p-value
GSK vaccine (Reference: non-GSK vaccine)	1.46	0.00	N/A	1.00	N/A	N/A	N/A	N/A
Vaccinated (Reference: Non-vaccinated)	N/A	N/A	N/A	N/A	1.35	0.50	3.21	0.52
Age	0.98	0.94	1.02	0.28	0.99	0.98	1.01	0.22
Gender: Male (Reference: Female)	1.20	0.14	9.99	0.86	0.74	0.41	1.30	0.30
Ethnicity: Asian (Reference: White)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ethnicity: Black (Reference: White)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ethnicity: Mixed (Reference: White)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ethnicity: Other (Reference: White)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ethnicity: Unknown (Reference: White)	2.04	0.10	17.36	0.55	0.64	0.35	1.15	0.14
IMD Score	0.91	0.69	1.04	0.36	1.00	0.97	1.03	0.88
Any high risk group	1.05	0.08	25.02	0.97	1.03	0.50	2.02	0.94
Surveillance method: EHR data mining (Reference: Enhanced passive)	N/A	N/A	N/A	N/A	0.61	0.21	1.76	0.36
Any concomitant vaccine	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table 56 – Tabular summary of multivariate logistic regression results for rash adverse events

Rash								
Population Outcome	Vaccinated patients AEIs within 14 days post vaccination				All registered patients AEIs/IDEs at any time			
	OR	LCI	UCI	p-value	OR	LCI	UCI	p-value
GSK vaccine (Reference: non-GSK vaccine)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Vaccinated (Reference: Non-vaccinated)	N/A	N/A	N/A	N/A	2.29	1.76	2.96	0.00
Age	1.00	0.98	1.01	0.59	0.98	0.98	0.98	0.00
Gender: Male (Reference: Female)	0.52	0.23	1.11	0.10	0.75	0.61	0.92	0.01
Ethnicity: Asian (Reference: White)	2.01	0.11	9.77	0.50	0.69	0.31	1.31	0.30
Ethnicity: Black (Reference: White)	N/A	N/A	N/A	N/A	0.43	0.02	1.92	0.40
Ethnicity: Mixed (Reference: White)	N/A	N/A	N/A	N/A	0.64	0.11	2.02	0.54
Ethnicity: Other (Reference: White)	N/A	N/A	N/A	N/A	0.52	0.03	2.31	0.51
Ethnicity: Unknown (Reference: White)	1.84	0.67	4.34	0.19	0.42	0.33	0.53	0.00
IMD Score	0.98	0.94	1.02	0.45	0.99	0.97	1.00	0.01
Any high risk group	0.88	0.30	2.95	0.82	2.22	1.75	2.81	0.00
Surveillance method: EHR data mining (Reference: Enhanced passive)	N/A	N/A	N/A	N/A	1.74	1.19	2.60	0.01
Any concomitant vaccine	N/A	N/A	N/A	N/A	0.86	0.14	2.74	0.83

Table 57 – Tabular summary of multivariate logistic regression results for general adverse events

General								
Population	Vaccinated patients				All registered patients			
Outcome	AEIs within 14 days post vaccination				AEIs/IDEs at any time			
	OR	LCI	UCI	p-value	OR	LCI	UCI	p-value
GSK vaccine (Reference: non-GSK vaccine)	1.52	0.33	6.41	0.57	N/A	N/A	N/A	N/A
Vaccinated (Reference: Non-vaccinated)	N/A	N/A	N/A	N/A	1.73	1.25	2.39	0.00
Age	1.00	0.98	1.02	0.92	1.00	1.00	1.01	0.61
Gender: Male (Reference: Female)	0.80	0.38	1.65	0.56	0.61	0.48	0.77	0.00
Ethnicity: Asian (Reference: White)	0.00	N/A	N/A	0.99	0.55	0.17	1.31	0.24
Ethnicity: Black (Reference: White)	0.00	N/A	N/A	1.00	0.68	0.04	3.03	0.70
Ethnicity: Mixed (Reference: White)	0.00	N/A	N/A	1.00	0.61	0.03	2.74	0.62
Ethnicity: Other (Reference: White)	0.00	N/A	N/A	1.00	1.66	0.27	5.26	0.48
Ethnicity: Unknown (Reference: White)	1.39	0.40	3.71	0.55	0.52	0.40	0.67	0.00
IMD Score	0.96	0.90	1.00	0.09	0.99	0.98	1.00	0.21
Any high risk group	0.99	0.30	3.90	0.98	1.40	1.05	1.88	0.02
Surveillance method: EHR data mining (Reference: Enhanced passive)	1.50	0.35	6.07	0.57	0.91	0.63	1.32	0.62
Any concomitant vaccine	0.00	0.00	N/A	0.99	0.00	0.00	0.00	0.96

Table 58 – Tabular summary of multivariate logistic regression results for neurological adverse events

Neurological								
Population	Vaccinated patients				All registered patients			
Outcome	AEIs within 14 days post vaccination				AEIs/IDEs at any time			
	OR	LCI	UCI	p-value	OR	LCI	UCI	p-value
GSK vaccine (Reference: non-GSK vaccine)	1.38	0.15	12.75	0.76	N/A	N/A	N/A	N/A
Vaccinated (Reference: Non-vaccinated)	N/A	N/A	N/A	N/A	1.45	1.11	1.89	0.01
Age	0.99	0.97	1.00	0.06	0.99	0.99	0.99	0.00
Gender: Male (Reference: Female)	0.46	0.21	0.93	0.04	0.44	0.36	0.54	0.00
Ethnicity: Asian (Reference: White)	N/A	N/A	N/A	N/A	0.66	0.32	1.21	0.23
Ethnicity: Black (Reference: White)	N/A	N/A	N/A	N/A	1.91	0.75	3.98	0.12
Ethnicity: Mixed (Reference: White)	N/A	N/A	N/A	N/A	0.86	0.21	2.27	0.79
Ethnicity: Other (Reference: White)	N/A	N/A	N/A	N/A	0.40	0.02	1.78	0.36
Ethnicity: Unknown (Reference: White)	0.42	0.07	1.42	0.24	0.46	0.37	0.56	0.00
IMD Score	1.00	0.97	1.03	0.84	1.01	1.00	1.02	0.01
Any high risk group	3.73	1.00	24.36	0.09	1.33	1.07	1.64	0.01
Surveillance method: EHR data mining (Reference: Enhanced passive)	2.47	0.29	21.03	0.37	1.53	1.05	2.29	0.03
Any concomitant vaccine	3.55	0.57	12.23	0.09	1.60	0.39	4.34	0.43

Table 59 – Tabular summary of multivariate logistic regression results for musculoskeletal adverse events, by method of surveillance

Musculoskeletal								
Population	Vaccinated patients				All registered patients			
Outcome	AEIs within 14 days post vaccination				AEIs/IDEs at any time			
	OR	LCI	UCI	p-value	OR	LCI	UCI	p-value
GSK vaccine (Reference: non-GSK vaccine)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Vaccinated (Reference: Non-vaccinated)	N/A	N/A	N/A	N/A	1.40	1.16	1.70	0.00
Age	1.00	0.99	1.01	0.77	1.02	1.01	1.02	0.00
Gender: Male (Reference: Female)	0.74	0.47	1.14	0.18	0.73	0.63	0.83	0.00
Ethnicity: Asian (Reference: White)	N/A	N/A	N/A	N/A	0.91	0.57	1.37	0.67
Ethnicity: Black (Reference: White)	N/A	N/A	N/A	N/A	0.60	0.15	1.58	0.38
Ethnicity: Mixed (Reference: White)	N/A	N/A	N/A	N/A	1.02	0.36	2.24	0.96
Ethnicity: Other (Reference: White)	N/A	N/A	N/A	N/A	0.78	0.19	2.05	0.67
Ethnicity: Unknown (Reference: White)	0.56	0.21	1.18	0.17	0.25	0.20	0.29	0.00
IMD Score	1.00	0.98	1.02	0.76	0.99	0.99	1.00	0.16
Any high risk group	3.57	1.22	15.25	0.04	1.08	0.90	1.29	0.42
Surveillance method: EHR data mining (Reference: Enhanced passive)	N/A	N/A	N/A	N/A	1.57	1.23	2.00	0.00
Any concomitant vaccine	0.78	0.04	3.61	0.81	1.20	0.51	2.40	0.64

Table 60 – Tabular summary of multivariate logistic regression results for local adverse events, by method of surveillance

Local								
Population	Vaccinated patients				All registered patients			
Outcome	AEIs within 14 days post vaccination				AEIs/IDEs at any time			
	OR	LCI	UCI	p-value	OR	LCI	UCI	p-value
GSK vaccine (Reference: non-GSK vaccine)	5.88	0.22	N/A	0.22	N/A	N/A	N/A	N/A
Vaccinated (Reference: Non-vaccinated)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Age	1.00	0.97	1.04	0.84	0.99	0.97	1.03	0.61
Gender: Male (Reference: Female)	0.15	0.01	0.84	0.08	0.25	0.04	0.94	0.07
Ethnicity: Asian (Reference: White)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ethnicity: Black (Reference: White)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ethnicity: Mixed (Reference: White)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ethnicity: Other (Reference: White)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ethnicity: Unknown (Reference: White)	0.96	0.05	5.52	0.97	0.19	0.03	0.81	0.04
IMD Score	1.03	0.95	1.08	0.43	1.01	0.94	1.06	0.77
Any high risk group	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Surveillance method: EHR data mining (Reference: Enhanced passive)	0.86	0.03	26.17	0.92	0.10	0.02	0.42	0.00
Any concomitant vaccine	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

8.4.3. Propensity matching

Propensity matching was carried out to reduce any bias differentiating the vaccinated and non-vaccinated groups. This was done retrospectively on the cohort of patients who were registered with the practices from week 35 to week 49. There may be scope to include date of presentation in a future iteration to see if this or another method could be used week-by-week to compare AEI/IDEs between vaccinated and non-vaccinated.

We used a propensity matching method to create a subset of the cohort (8,006 patients), with half vaccinated and the other half unvaccinated. Each half had the same probability of receiving the seasonal influenza vaccination based on their age, gender, and high risk group category. The propensity-matched odds ratios suggest that vaccinated patients were more likely to attend their GP than non-vaccinated for AEIs/IDEs. The only exception is for AEIs within the sensitivity/anaphylaxis broad category (OR 0.88, 95%CI 0.30-2.49). However, as the confidence intervals cross parity (i.e. span across 1), we cannot be certain of the direction of the relationship. It is plausible that the group of patients reporting these events may be less likely to be vaccinated.

Table 61 **– Tabular summary of odds ratio after using a propensity matching method, by adverse event category**

Population	All registered patients		
Exposure	Vaccination status (Vaccinated or not vaccinated - Reference: not vaccinated)		
Outcome	AEIs/IDEs at any time		
	OR	LCI	UCI
All	4.34	3.83	4.93
Respiratory	3.62	2.97	4.43
Gastrointestinal	5.50	3.71	8.48
Fever / Pyrexia	5.08	3.94	6.64
Sensitivity / Anaphylaxis	0.88	0.30	2.49
Rash	3.82	2.59	5.83
General	2.77	1.79	4.43
Neurological	3.11	2.10	4.75
Musculoskeletal	4.53	3.43	6.07
Local	N/A	N/A	N/A

9. Study feasibility assessment

The key elements of our feasibility assessment are as follows:

Timeliness:

- To assess the timeliness of vaccination data
- To assess the timeliness of AEI reporting, both in the EHR data mining and the enhanced passive (yellow card) surveillance systems

Completeness:

- To assess the completeness of vaccination data
- To assess the completeness of AEI reporting, both in the EHR data mining and the enhanced passive (yellow card) surveillance systems

Accuracy:

- To assess whether the rates of the most frequently reported events are compatible with expectations from published rates in a comparable population

9.1. Timeliness

The key element of timeliness is the delivery of a weekly report, and feedback to practices to ensure that these data are of quality. However, there are a range of other factors that can affect this.

1. Recruitment of practices
2. Ethical approvals
3. University contractual timelines
4. Starting the observation period from the week that vaccines are available
5. Collection of weekly practice surveillance data and feedback to practices about data quality
6. Producing the weekly report
7. Direct collection of hospital data
8. Lag between event and recording data in NHS record systems

9.1.1. Recruitment of practices

Any further recruitment of practices should be started in June, at the latest. Practices do not meet much during August, and some start vaccination as soon as the receive vaccine stock in September. The recruitment of the practices is also a key step that enables a number of ensuing steps, such as the initiation visits and set-up of data collection systems that are key to a swift start to the project. Delays in practice recruitment, particularly trying to ensure representativeness of vaccine brands, meant that this study produced an initial weekly report eight weeks after the major vaccination clinics started.

9.1.2. Ethical approvals

Where no major ethical issues are raised, the study is eligible for proportionate review, which has a decision lead time of about 2 weeks. However, the completion of an ethics application and gathering of the necessary documents can take up to a month. Often, practice management requires evidence of ethical approvals, before agreeing to participate in the study, so it is essential that this approval is secured early in the year.

9.1.3. University contractual timelines

Achieving legal and financial agreements tend to take several weeks or even a few months. This should be built into our lead time.

9.1.4. Starting the observation period from the week that vaccines are available

The initiation of practices for data collection should start prior to their first flu immunisation being given. Whilst the standard surveillance for influenza starts in week 40, we recommend starting in week 35. This allows enough time for the set-up of the automated data collection system, and for the practice staff to become acquainted with the need to code consultation data accurately and promptly after a consultation, or after receiving a reporting card.

9.1.5. Collection of weekly practice surveillance data and feedback to practices about data quality

We have demonstrated the feasibility of collecting weekly data (weekly cross-sectional data) specific for this programme. This includes data for all registered patients attending the practice. The software programming (we use SQL for database management and Tableau as a business intelligence software) takes around 6 weeks to design according to the study's specific needs; once set up, these reports run efficiently. For instance, the programming set up by the Research Group at the [redacted] processes 1.3 million patients records in about 40 to 90 minutes each week to produce the [redacted] weekly infectious disease and morbidity report[7]

These reports could produce a timely snapshot of AEIs. We would like to report them for the non-vaccinated as many of them may occur unrelated to vaccine exposure. Additionally, using the same set-up but with a different design, we can produce weekly feedback to each practice to advise them on their recording practices, compared to the rest of the sample. This helps keep clinicians focused on the need to record AEIs in an accurate and timely manner.

Weekly reports do not always run completely because a large number of communications take place with general practice systems. A large number of reports and updates are flowing in and out of practices. These can block or truncate our extract, we lose 3%-5% of practices per week from the [redacted] surveillance system for this reason. We had this problem over the last few weeks of this study with two of the practices, so we visited the practices and collected these data manually. Longer term, the surveillance system should have a pool of practices where a small number can drop in and out of the weekly report – but all would be included in the mid-season and end of season report.

9.1.6. Producing weekly reports

The primary focus of this programme will be the production of consistent weekly reports that can give in season feedback as to levels of AEIs, and be able to differentiate signal in AEIs from that occurring in both AEI and IDE. However, whilst much data are available in near real time, others are not and may benefit from further detailed review when more information is available (e.g. precise diagnosis that underlies a hospital admissions).

We propose, in addition to the weekly reports, there might be other optional reports. These would comprise: a mid- and end of season cohort study comparing: (1) For vaccinated people: Specific brand with other brands; and (2) For the whole practice population. This should be

[7] http://www.rcgp.org.uk/clinical-and-research/our-programmes/research-and-surveillance-centre.aspx

published every season, according to a pre-defined format. The protocol for analysis should also be published, once this process is established. This is similar to the process established for the [redacted] whereby weekly reports are produced throughout the season, and a mid- and end of season reports are also published.

9.1.7. Direct collection of hospital data

The principal output of this study and the feasibility report is the weekly report and the data derived from it. However, we see the cohort studies at the mid and end of season points as opportunities to reflect on what we are reporting and informing how we would improve the weekly data report. For example, a cluster of admissions with rash or high fever in children post-vaccination may be hard to interpret without details about whether they were all discharged within 24 hours or had longer lengths of stay. Better matching with non-vaccinated would help address this further.

Direct collection of hospital data (official name is Hospital Episode Statistics – HES) could add to this study as it would make data about admission more reliable than that recorded in the primary care record. However, these data are not timely – coming about 3 months later in areas. They could form a feature of the end of season report, as most influenza vaccine is administered in the autumn. HES can also be linked to Office of National Statistics (ONS) death data. Although likely to be rare, it may be important to investigate deaths linked to an AEI following vaccination.

9.1.8. Lag between event date and recorded date in NHS record systems

In routine primary care data, the date of recording may differ from the date of the event. This rarely applies to vaccination status, though it can lag by a few days. Typically, GPs apply the vaccine administration code on the day of vaccination, but may add the prescription codes some days later, particularly when the vaccination clinic is at a weekend. This also applies to diagnoses that emerge from investigations or come from hospital admissions or clinics.

Sometimes GPs may add an entry to the patient's record several weeks after the date of the event. Most of the AEIs are recorded on the day in real time. However, sometimes data from a hospital report or test leads the GP to change the diagnosis; generally this is from a more generic to a specific one. For example, a GP may see a patient with a cough, thinking it is probably an upper respiratory tract virus; however, because of a smoking history, the GP may order a chest X-ray. The delay in the X-ray report showing pneumonia reaching the GP can be 10 days after the initial consultation. The GP would then phone the patient to institute treatment and follow-up, and then code the pneumonia event, changing the diagnosis for the initial consultation.

Therefore, it is expected that each week there would be a small variation in the AEIs/IDEs and vaccination rates from previous weeks, as new data is recorded. A final report produced with data extracted 6 weeks from the end of the study would contain as complete data as can be obtained from the GP recorded data. Data entry of the results from the yellow card will also represent a delay in the timeliness of the data, as administrative staff in a general practice will record the event date (the date when the AEI occurred, as reported by the patient).

9.2. Completeness

There are several perspectives of data completeness. Our focus on the completeness is on vaccine exposure data. AEI data recording is also crucial for this study. The wider range of considerations includes:

1. Practice denominator
2. High risk individuals eligible for influenza vaccine
3. Vaccine exposure in enhanced passive surveillance and EHR data mining arms
4. Brand coverage in enhanced passive surveillance and EHR data mining arms
5. AEI recording in enhanced passive surveillance and EHR data mining arms

9.2.1. Practice denominator

The practice denominator is one of the most reliable elements of English primary care records. Patients are registered with a single GP and have a unique NHS number. Death, registration with another practice, or emigration automatically results in deregistration and transfer of records. However, death and deregistration are not strictly applied, and linkage to Office of National Statistics (ONS) data would be needed to ensure we have accurately recorded cause of death.

9.2.2. High risk individuals eligible for influenza

A pay-for-performance scheme (the Quality and Outcomes Framework, QOF) has impacted positively on the recording of chronic diseases in UK primary care computer systems. This group is readily identifiable in GP records. Requiring one year's registration with the practice for inclusion in the cohort, means that even patients who have newly transferred will have had time for their previous records to "catch up" and be included.

9.2.3. Vaccine exposure

Most vaccines, particularly to children and high risk adults, are personally administered by their GP. This means that data about vaccine exposure will be largely complete. However, there are increasing trends toward plurality of vaccine providers – pharmacists, NHS and other occupational health schemes. In a long term surveillance network, we would want to feedback to practices their recording of personally administered as well as non-personally administered vaccines, and to ensure such data were coded into the EHR in a brand specific way.

We compared the completeness of vaccinated data of the cohort during the study period, with the [redacted] network for the same weeks in 2014. For the same period in the [redacted] the vaccination rate was slightly higher, although the differences are not significant (Table 62). This indicates that, for recording of vaccination, the sample of practices taken for this study was as representative as the [redacted] network, which is a gold standard sentinel network.

Table 62 - Vaccine coverage in the pilot practices compared with the [redacted] coverage for 2014

	Vaccination status							
	Pilot practices 2015				[redacted]etwork 2014			
	Vaccinated		*Non vaccinated*		*Vaccinated*		*Non vaccinated*	
Total	14801		56606		238519		855833	
	20.73%		79.27%		21.80%		78.21%	
	20.43%	21.03%	78.97%	79.57%	21.72%	21.88%	78.14%	78.29%

9.2.4. Brand coverage

The use of the GSK brand influenza vaccine during this vaccination season would not necessarily predict that the practices would use the same brand the following season. Individual general practices are businesses that can select a brand of influenza vaccine for a range of reasons. To ensure brand coverage we propose the following:

1. A large network of EHR data mining practices is recruited. They will provide feedback about AEIs and vaccine exposure each year (to ensure data quality), and provide a pool of practices from which we can draw enhanced passive surveillance practices
2. Enhanced passive surveillance practices are recruited to provide brand-specific enhanced passive surveillance for one or more vaccine manufacturers.

9.2.5. AEI recording

Practitioners generally see people for a 10-minute consultation; they enter data into the EHR during the consultation, generally while the patient is there. Some data will be coded, and some will be free-text; we only extract the coded data. The main issues in completeness of data stem from the Read Codes used when querying the data. As an example, we recommended to GPs to use a particular code when recording fever or the temperature and when querying the data for this code, we found that temperature recording was very incomplete.

The issue was due to GPs having used a different code to record temperature; this was a code to indicate method of taking the temperature (orally, rectally, axillary), which is more relevant from a clinical viewpoint. Once we queried the data using this code, we found a higher level of temperature recording. This could have happened for many of the variables considered in this report, so it is essential to have a clear process of code determination for the main AEIs of interest, in order to ensure complete capture of the data.

9.3. Accuracy

The principal area of accuracy is ensuring we are capturing AEIs/IDEs reliably. The accuracy of the data were good (Table 62). Rates of the most frequently reported AEIs in the cohort are similar to the pattern reported across >1.3million patients in the [redacted] practices for week 35 to 49 in 2014. However, overall, a higher proportion of influenza vaccinated people in the [redacted] network presented with AEIs (14.1%, 95%CI 13.9-14.2), compared with the cohort in 2015 (11.9%, 95%CI 11.4-12.4). Similarly, there was a higher proportion of non-vaccinated patients in the [redacted] network presenting with AEIs (7.4%, 95%CI 7.3-7.4), compared with the cohort in 2015 (5.2%, 95%CI 5.0-5.4).

Table 63 - AEI rates in the pilot practices compared with the [redacted] rates for 2014

	AEI/IDE at any time							
	Feasibility study practices 2015				[redacted] Network 2014			
AEI/IDE category	*Vaccinated*		*Non vaccinated*		*Vaccinated*		*Non vaccinated*	
Any AEI	1761		2939		33601		63168	
	11.90%		5.19%		14.09%		7.38%	
	11.38%	12.42%	5.01%	5.38%	13.95%	14.23%	7.33%	7.44%
Any Respiratory	652		965		12255		21059	
	4.41%		1.70%		5.14%		2.46%	
	4.08%	4.74%	1.60%	1.81%	5.05%	5.23%	2.43%	2.49%
Any Gastrointestinal	201		232		3181		5158	
	1.36%		0.41%		1.33%		0.60%	
	1.18%	1.55%	0.36%	0.46%	1.29%	1.38%	0.59%	0.62%
Any Fever / Pyrexia	438		739		8541		17732	
	2.96%		1.31%		3.58%		2.07%	
	2.69%	3.24%	1.21%	1.40%	3.51%	3.66%	2.04%	2.10%
Any Sensitivity / Anaphylaxis	16		37		377		865	
	0.11%		0.07%		0.16%		0.10%	
	0.06%	0.16%	0.05%	0.09%	0.14%	0.17%	0.09%	0.11%
Any Rash	150		250		2998		6387	
	1.01%		0.44%		1.26%		0.75%	
	0.86%	1.18%	0.39%	0.50%	1.21%	1.30%	0.73%	0.76%
Any General	126		187		2176		3923	
	0.85%		0.33%		0.91%		0.46%	
	0.71%	1.00%	0.28%	0.38%	0.87%	0.95%	0.44%	0.47%
Any Neurological	133		357		2431		6944	
	0.90%		0.63%		1.02%		0.81%	
	0.75%	1.05%	0.57%	0.70%	0.98%	1.06%	0.79%	0.83%
Any Musculoskeletal	357		543		7608		10987	
	2.41%		0.96%		3.19%		1.28%	
	2.17%	2.66%	0.88%	1.04%	3.12%	3.26%	1.26%	1.31%
Any Local	12		0		3		2	
	0.08%		0.00%		0.00%		0.00%	
	0.04%	0.13%	N/A	N/A	0.00%	0.00%	0.00%	0.00%

We further describe issues related to accuracy under the following headings:

1. Reliability of data recording
2. Validity
3. Reducing bias

9.3.1. Reliability of data recording

The reliability of data recording in English primary care is good, and internationally, English primary care data are used for research more than other data systems. However, we know that by using feedback and education we can improve the reliability of data recording. Whilst we

have most experience of improving data quality in chronic diseases, we have been applying these methods to the [redacted] databases to improve consistency.

We adopted both an educational intervention (known as Audit Based Education, ABE[41 42]) and a behavioural change approach, based on the COM-B model (a simple model suggesting that capability, motivation and opportunity are all needed to affect behaviour change); we have applied this in a range of contexts[43]. We generally support programmes with online learning and opportunities for participating practices to take part in clinical audits, as this helps maintain practitioners' interests and therefore also the reliability of data recording.

9.3.2. Validity

Our guidelines for GP data recording is that the doctor should record what he/she thinks the diagnosis is. Within the [redacted] we encouraged GPs (and other primary care professionals) to code "influenza like illness", where they think this is the diagnosis. We want them to avoid symptom codes, unless they are really unclear as to the diagnosis. This approach has led to the [redacted] being the gold standard surveillance network.

An important facet of our network and an enhanced surveillance group is that we know exactly who the practices are. In a long term surveillance network we would appoint a dedicated practice liaison officer who would build a personal relationship with the practices, and be able to call them if an unusual code was recorded or there was a possible serious AEI. In a longer term project, we could develop specific reporting tools. Extending from the yellow card scheme to other reporting systems may improve the reliability as well as the validity of the AEI recording process.

9.3.3. Reducing bias

There are significant differences between the EHR data mining and enhanced passive surveillance systems. It is difficult to compare brand-specific with non-brand specific vaccination data, when both brand specific practices (GSK vaccine) were in the enhanced passive surveillance arm (i.e. patients receiving yellow cards), and the comparator practices (non-GSK vaccine) are largely under the EHR data mining arm.

In the enhanced passive surveillance arm, there may be a greater propensity to record some AEIs in the vaccinated group. This happens because only vaccinated patients are provided with yellow cards and encouraged to record their AEIs. This means that under this system, only vaccinated patients would be receiving yellow card and would be encouraged to report any AEIs in this manner, while non-vaccinated patients would report any AEIs/IDEs in a method akin to that of the EHR data mining arm.

Assuming that the enhanced passive surveillance method would result in an increase of some reported AEIs (as patients are prompted to report), this would represent a bias between vaccinated and unvaccinated patients in this arm of the study. However, whilst practices reported increase reporting of local reactions via the yellow card scheme, the concern and focus of the staff in those practices was on the cards, not solely on EHR data quality. EHR data quality was the sole focus of the practice staff in the EHR data mining arm. Different collection systems may bias data collection (e.g. younger people may use online systems more).

9.4. Summary

We have demonstrated the feasibility of setting up a network to provide timely brand-specific data about AEIs after an influenza vaccine. We have a registration-based GP system with a reliable denominator. We can capture brand-specific influenza vaccination data with the same degree of completeness as the [redacted] network, which is used as a data source by Public Health England for influenza vaccine effectiveness studies. The completeness of our AEI data appears to be equivalent to that of the [redacted] We can use the technologies developed at the [redacted] for [redacted] weekly reports to provide timely information. We will work to continually improve the quality of our output, including the use of better statistical approaches to help detect signal in these data.

It would be possible to build on this study and this existing network of practices and create a practice network to meet EMA requirements. Whilst there have been a number of studies of setting up vaccine safety, or active vaccine surveillance systems[44 45], none have used a pre-specified AEI list such as that provided by EMA for this study. As a Research Group, we would be ready to advance this. Keeping the learning about lead time, processes, and connections up-to-date and active would facilitate the development of this network.

10. Discussion

10.1. Main findings

- **Subjects and setting:** The recruitment of practices led to a population where the age-sex profile was largely representative of the English population, but the ethnicity and deprivation scores were not.
- **Vaccine exposure:** Vaccination exposure rates were generally in line with published national rates, although not when disaggregated by risk groups, and with those reported by the [redacted] network in 2014.
- **Surveillance method:** The enhanced passive surveillance process led to higher reporting of some AEIs (particularly local symptoms), using yellow cards given to subjects at the time of vaccination. This was an effective way to achieve higher reporting, at low cost. However, the response rate to the yellow card was low (2% of cards distributed, and 1.2% of vaccinated patients overall), and the rate of AEIs reported using this method was lower than that achieved through EHR data mining. Nonetheless, it was complementary, as some AEIs were only reported through this route. Practices involved in enhanced passive surveillance (handing out yellow cards) may have had lower EHR data quality; this certainly applied to one. They will need to ensure that EHR data recording and data quality match data quality standards.
- **Outcome measure – brand specific AEIs:** We have developed a method that can report rates of brand specific AEIs. We did not detect any major differences between GSK and the other pooled vaccine brands. However, there were some differences in some of the groupings of AEI, as set out in detail above. We claim only to have demonstrated feasibility of obtaining this data, but not necessarily to have made valid comparisons.
- **Outcome measure – detecting AEIs in vaccine exposed:** Rates of AEI (within 14 days post vaccination) in the vaccinated group were around 3%, with around 1% of these being respiratory conditions. Logistic regression showed that men who have been vaccinated present less with AEIs.
- **Outcome measure – background rates of AEIs/IDEs in the non-vaccinated population:** Propensity matching suggests that being vaccinated is associated with higher rates of presentation with AEIs/IDEs; in particular, for respiratory symptoms. Background rates of all AEIs/IDEs are around 5%, with respiratory disease and symptoms accounting for 2% (for a 15-week observation period). Our exploration of IDEs in the non-vaccinated population did not provide the insights we hoped. However, we remain convinced that these methods can be developed further. The goal is to be able to review week-by-week AEIs and IDEs in a matched population of vaccinated and non-vaccinated patients. The underlying hypothesis is that any signals in the vaccinated population also seen in the non-vaccinated, are unlikely to have a vaccine-related aetiology (i.e. a simultaneous rise in AEI and IDE is less likely to be associated with vaccination). Conversely, differences in between the two population, may indicate the significance of an AEI signal in the vaccinated population.

10.2. Strengths

- **Subjects and setting:** The Research Group has good connections that would enable it to successfully recruit practices to studies. We can adjust recruitment to gain a representative sample, probably by recruiting more inner city practices. Practices are likely to engage more with longer term studies.

- **Vaccine exposure:** Most vaccination is carried out within UK primary care, and for most age-groups and risk-groups. We know the specific brand for all practice administered vaccines (including batch number), and can improve information capture for the minority administered elsewhere.
- **Surveillance method:** Enhanced passive surveillance was shown to be easily deployable, with over 4000 cards distributed. This can be extended in future years. Enhanced passive surveillance, although also requiring manual data entry, does provide a second and more immediate route for data reporting. Because the MRHA have a long established yellow card scheme – practices instantly understood what this was for.
- **Outcome measure – brand specific AEIs:** Even though the GSK brand vaccines were only administered in the enhanced passive surveillance practices, there was not a significantly higher rate of AEIs detected. However, this study does not claim to report this as a key finding, as we are underpowered to draw such a conclusion. However, the feasibility of extracting such data, has been demonstrated.
- **Outcome measure – detecting AEIs in vaccine exposed:** Practices were happy to use our recommended Read code list for AEI/IDEs and also at being prompted to use this list if we perceived gaps in their data quality.
- **Outcome measure – background rates of AEIs in the non-vaccinated population:** We consider it is really important to ascertain background rates so that it is possible to give the best possible interpretation of the AEIs seen in the vaccinated population. Given that the extract and data processing are set-up, this has minimal extra costs. It would also allow us to know whether any sudden rise in AEIs is not confined to the vaccinated population. The comparison reported in this report demonstrates it is feasible to collect these data; but we do not demonstrate a satisfactory method for making a comparison. We see propensity to consult and practice coding factors as likely to be important when establishing this.

10.3. Limitations

- **Subjects and setting:** This study had the limitation of having all of the practices using the GSK vaccine in the enhanced passive surveillance arm. In future, the distribution of brand-specific practices needs to be more balanced, if more than one surveillance method is being used.
- **Vaccine exposure:** Though the overall rate of vaccine exposure matched published national rates and [redacted] network rates for previous years, when these were disaggregated into specific risk groups, the rates in this pilot were lower. This could have been due to the data extraction of risk group data, or due to a data quality issue at the level of the practices. Both of these potential sources must be approached in future studies, by creating validated code lists to extract risk group data, and by providing continual feedback to practices regarding their vaccination data.
- **Surveillance method:** The methods used were enhanced passive surveillance and EHR data mining. The data were initially extracted week-by-week as near real time data were needed to detect any potential signal. The limitations of cross-sectional data are well described:

> *"Although a cross sectional study can be very suggestive of a possible risk factor or risk factors for a disease, when an association is found in such a study, given the limitations in establishing a temporal relationship between exposure and outcome, we rely on cohort and case-control studies to establish etiological relationships"*[46]

Whilst we feel that there are limitations in the cross sectional data, we feel these can be mitigated by the subsequent cohort study. A cohort is more likely to give reliable incidence rates (Table 64).[47]

Table 64 – Contrasting the contribution and analytical outputs of cross-sectional and cohort studies (after Bhopal, 2002):

	Cross sectional	*Cohort*
Main contribution	*Major contribution to burden of disease, substantial contribution to analysis of associations and may confirm or spark hypotheses*	*Major contribution to both burden of disease (incidence) and causal analysis*
Analytical output	*Main output is prevalence though other measures including the odds ratio are possible (not the relative risk)*	*Incidence rate and the relative incidence, i.e. relative risk*

We have set out some of the limitations of data extracted in near real time, though we accept that this is important for this type of surveillance. There can be a delay between event and recording date in GP data. Only around two-thirds of people vaccinated in enhanced passive surveillance practices were given a yellow card; though there was a consistent 2% response rate. This is because some vaccination occurred earlier than our planned start week and because recording the yellow card data into the EHR was a new process for practices. Enhanced passive surveillance costs more, but it is possible that this could be subsidised by NIHR through its CRNs. One enhanced passive surveillance practice (non-GSK) recorded less AEIs than they had yellow cards returned. We can feedback and improve such data quality issues.

- **Outcome measure – brand specific AEIs:** We started producing a weekly report within 8 weeks of the first major vaccination clinics. The coding and extract routines to do this can be reused and we could make a more timely start next year. As mentioned before, there was a large bias in comparing GSK vaccines with other brands, due to both GSK vaccine practices being part of the enhanced passive surveillance arm. Our data extract system is not completely reliable, and the data extraction process for two practices failed in the later weeks of the report, and we had to manually collect this data, to complete the report on time. Collecting from a bigger number of practices and over a larger number of weeks would remove this problem.
- **Improving the statistical analysis of the weekly cross-sectional surveillance data:** We could use more sophisticated methods to look for signal in the weekly surveillance data. Techniques such as control chards or check sum charts might add to our ability to detect signal.
- **Outcome measure – detecting AEIs in vaccine exposed:** We needed to constantly reassure practitioners that recording an AEI was not ascribing a causal link. The idea of an AEI, in many practitioners' minds, implied a causal link to vaccination. We have had to emphasise that these are "possible AEIs" and that GPs are not ascribing causation, merely recording events, for which the statistical analysis may find a probability of a causal link. GP recording of hospital admissions may be unreliable, but this could be overcome by linking to hospital data (HES) and, if thought important, Office of National Statistics (ONS) data for

cause of death. However, HES data is not obtainable on a near-real-time basis, as is the case for the primary care data.

- **Outcome measure – background rates of IDEs (AEIs) in the non-vaccinated population:** The different approaches may cause confusion. The weekly reports represent a repeated cross-sectional analysis reporting two different set of rates. One for the vaccinated and one for the non-vaccinated population. The limitation of including both these rates in the weekly report was that the groups did not match (neither in numerator nor denominator definitions), particularly in relation to the follow-up period. Once the methods of analysis are refined, it would be possible to generate an XML or other weekly generation of raw data (in addition to the report). This could provide EMA and other stakeholders a regular snapshot that could be used by manufacturers. A possible format for this would be to use the European Surveillance System (TESSy) report format[8]; as developed by the European Centre for Disease Control (ECDC). The Research Group at the [redacted] create these on a weekly basis, for the report on infectious and communicable diseases.

10.4. Feasibility

The feasibility report shows that enhanced passive surveillance supporting EHR data mining can be set up based on the learning from this year, and it can be potentially enhanced and enriched. Standardising reporting according to pre-published protocols would further strengthen it. We would want to recruit practices in excess of the numbers needed for the study so that we can ensure we have the right balance of vaccine manufacturers.

11. Conclusions and recommendations

UK primary care with its registered lists, highly computerised practices, and being where most influenza (and other vaccination) takes place is an ideal location for implementing the enhanced surveillance required by EMA. The [redacted] at the [redacted] has the technologies, and the scientific, clinical, and analytical ability to run such a network.

The AEIs that the EMA are interested in monitoring following immunisation have an incidence of around 3% in UK primary care in the two weeks following vaccination. Enhanced passive surveillance, with a simple yellow card scheme, appears to add to EHR data mining. The advantages of the yellow card over simply relying solely on EHR data mining surveillance is that this method captured underreported conditions (such as local symptoms) and could be targeted at populations with a lower propensity to consult (such as men).

It is feasible to use this approach to compare rates of AEIs across vaccine brands. It is also possible to report rates of AEIs/IDEs reported in vaccinated compared with non-vaccinated people. This may prove useful to identify whether a signal is arising from a vaccine, or from a disease outbreak in the wider population. We stress that we have reported feasibility, not difference in rates; whilst the AEI/IDE comparison in this report is important, we need to develop methods that provide a better matched population.

[8] Information about ECDC TESSy based indicator system at:
http://ecdc.europa.eu/en/activities/surveillance/Pages/index.aspx

We see enhanced passive surveillance combined with EHR data mining as the right way to take the EMA requirement forward. The bias in who is likely to consult a GP with a possible AEI, means that the EHR data mining approach may not be representative. To execute this, we need to have a relationship with a pool of practices who can improve their data quality and operationalise the yellow card system and any subsequent developments. Each year, after the practice has made its own choice about brand of vaccine for the coming season and have passed data quality checks, we would select practices to be in the enhanced passive surveillance group or remain in the EHR data mining only pool.

This study demonstrates that it is feasible to set up a surveillance system that would rapidly detect brand specific AEI signals for influenza vaccinated patients. We can produce weekly reports from complex data. We recommend that the enhanced passive surveillance, in addition to the EHR data mining is used. We recommend this because our feasibility study infers that groups with a greater propensity to consult may be overrepresented (and other groups with less propensity to consult, may be underrepresented), and some AEIs (such as local symptoms) may be reported more using enhanced passive surveillance. The yellow card approach was readily and rapidly understood by practices.

Although our comparisons between AEIs and IDEs was not as useful as we had hoped, we feel that the collection of IDEs amongst non-vaccinated patients should continue; with better week-on-week matching it should provide useful information. We believe it will be possible to use IDEs in the non-vaccinated population to infer whether a signal in AEIs in the vaccinated population is likely to have a vaccine-related aetiology.

It is feasible to set up a weekly near real-time reporting, using an enhanced passive and EHR data mining surveillance system, to detect EMA-specified AEIs across specific brands.

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Appendix A

[redacted]

Post-authorisation safety study of influenza vaccine

Key Statistics:

Week Number/Year…….42/2015
Week Starting - Ending……..…12/10/2015 - 18/10/2015
No. of Practices……9
Population…….80727 (9397 vaccinated)

Post-authorisation safety study:

The European Medicines Agency (EMA) has set out new requirements for influenza vaccine safety surveillance that all Marketing Authorisation Holders (MAHs) providing vaccines in the EU must address. This pilot, funded by Glaxo-SmithKline and conducted by the [redacted] explores the use of routinely collected data in the UK to provide timely and relevant information on influenza vaccine safety.

UK primary care is highly computerised, though the major suppliers have different data models, coding systems, and methods of data access. This pilot study demonstrates the feasibility of drawing together the heterogeneous data from different brands of computer system into a single report format.

Key messages:

Vaccine exposure:

Vaccine exposure rates for all ages have **increased** from **9.03 in week 41** to **11.86 in week 42**.

Practice types:
Enhanced passive practices gave vaccinated patients a card to prompt reporting; Electronic Health Record data mining (EHR data mining) practices have findings reported from routine data.

Possible adverse events in the vaccinated population by Enhanced passive and EHR data mining practices (per 100,000 patients):

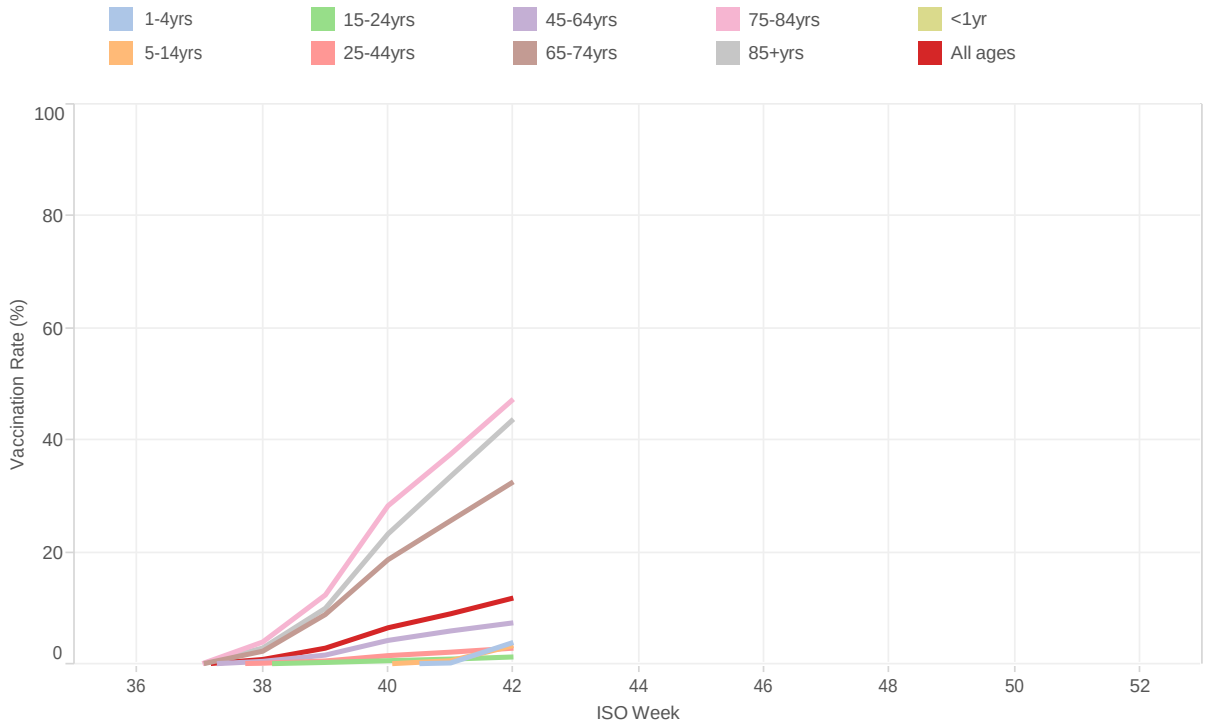
- **Fever/Pyrexia :** Enhanced passive rate was **327.6** in week 41 compared with **285.7** in week 42. EHR data mining rate was **401.8** in week 41 compared with **402.3** in week 42.
- **Gastrointestinal :** Enhanced passive rate was **93.6** in week 41 compared with **57.1** in week 42. EHR data min-ingrate was **146.1** in week 41 compared with **402.3** in week 42.
- **General symptoms :** Enhanced passive rate was **140.4** in week 41 compared with **400.0** in week 42. EHR data mining rate was **36.5** in week 41 compared with **160.9** in week 42.
- **Local symptoms :** Enhanced passive rate was **46.8** in week 41 compared with **171.4** in week 42. EHR data mining rate was **36.5** in week 41 compared with **0.0** in week 42.
- **Musculoskeletal :** Enhanced passive rate was **187.2** in week 41 compared with **628.6** in week 42. EHR data mining rate was **365.2** in week 41 compared with **603.4** in week 42.
- **Neurological :** Enhanced passive rate was **93.6** in week 41 compared with **0.0** in week 42. EHR data mining rate was **182.6** in week 41 compared with **80.5** in week 42.
- **Rash :** Enhanced passive rate was **187.2** in week 41 compared with **57.1** in week 42. EHR data mining rate was **146.1** in week 41 compared with **120.7** in week 42.
- **Respiratory/Miscellaneous :** Enhanced passive rate was **748.7** in week 41 compared with **457.1** in week 42. EHR data mining rate was **620.9** in week 41 compared with **764.3** in week 42.
- **Sensitivity/anaphylaxis :** Enhanced passive rate was **0.0** in week 41 compared with **57.1** in week 42. EHR data mining rate was **0.0** in week 41 compared with **40.2** in week 42.

Comment:

The proportion of the practice population vaccinated increased this week. The most common possible adverse event categories this week were respiratory/miscellaneous, musculoskeletal, and fever/pyrexia.

Influenza vaccine exposure rates

(A) Cumulative vaccine exposure rates: All age groups, 2015 *



* The vaccination exposure rates are a percentage of all registered patients in the pilot practices.

(B) Cumulative vaccine exposure rates: All age groups, by vaccine brand, 2015 *

	GSK vaccine	Non-GSK vaccine
<1yr		
1-4yrs	0.00	4.71
5-14yrs	0.07	4.08
15-24yrs	1.45	1.33
25-44yrs	2.73	2.94
45-64yrs	7.74	7.37
65-74yrs	36.07	31.69
75-84yrs	54.04	45.38
85+yrs	43.86	43.81
All ages	13.96	11.37

* The GSK vaccine rates are based on the vaccine exposure rates in 2 out of 9 of the pilot practices.

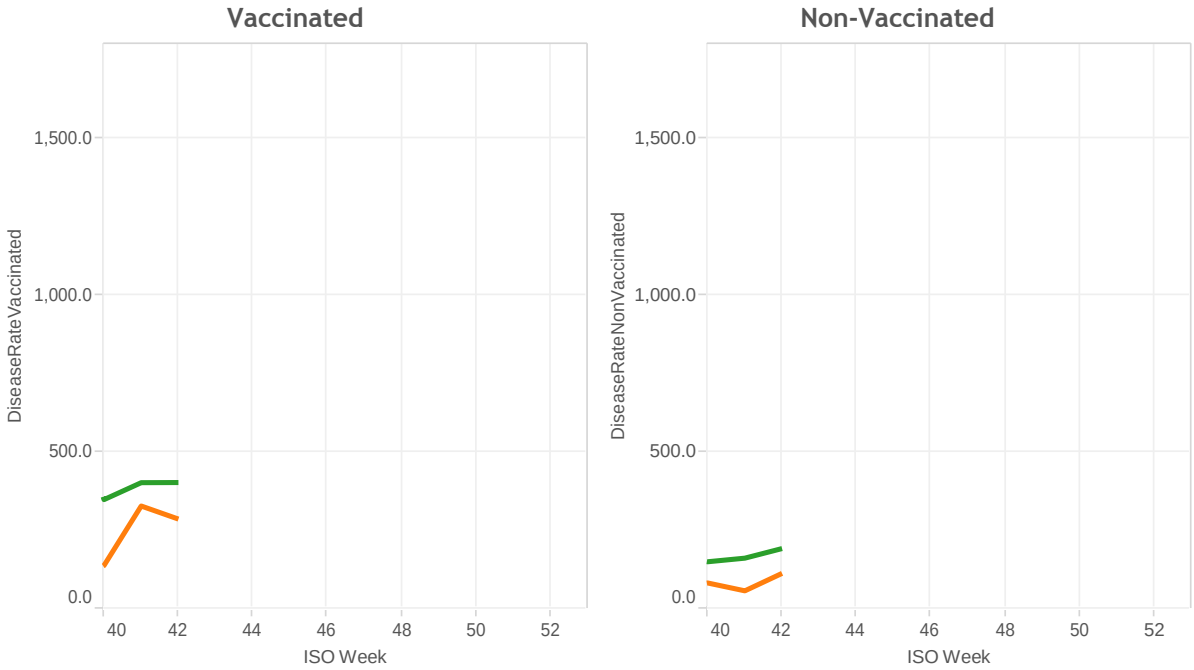
(C) Key denominators

	Registered Patients	Vaccinated Patients	Vaccination Rate
Non-GSK vaccine	64,093	7,287	11.37
GSK vaccine	15,120	2,110	13.96
Grand Total	80,727	9,397	11.86

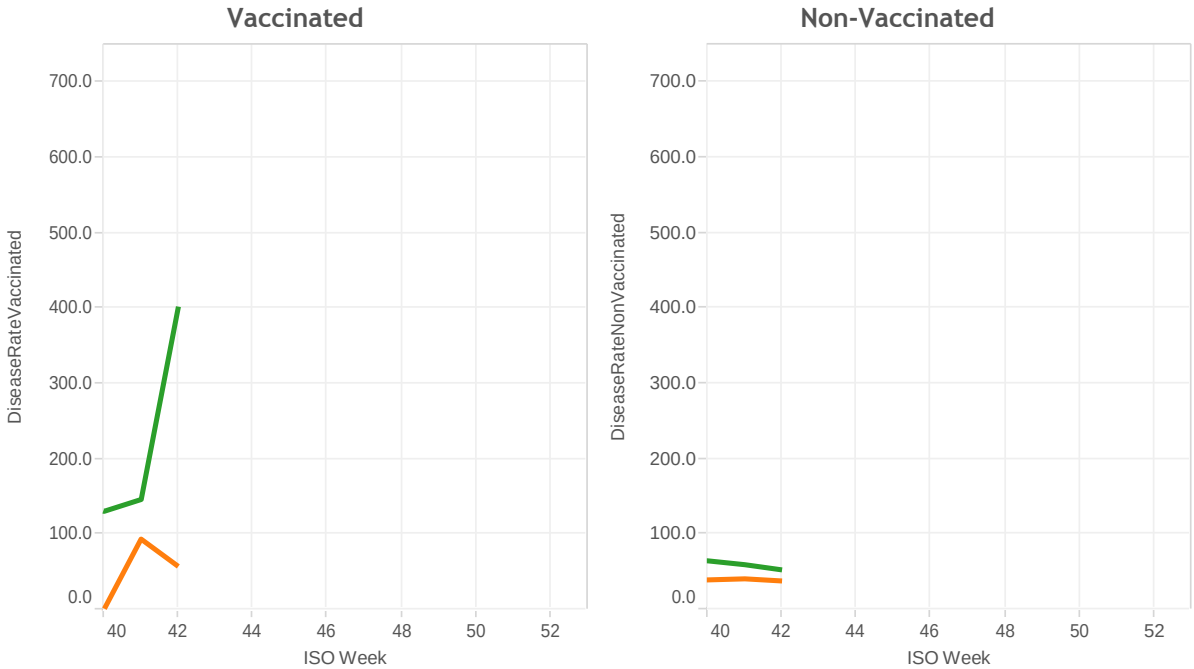
	Registered Patients	Vaccinated Patients	Vaccination Rate
EHR data mining	50,794	4,911	9.67
Enhanced passive	28,419	4,486	15.79
Grand Total	80,727	9,397	11.86

Possible adverse event rates by EMA surveillance condition

(D) Fever/Pyrexia by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015

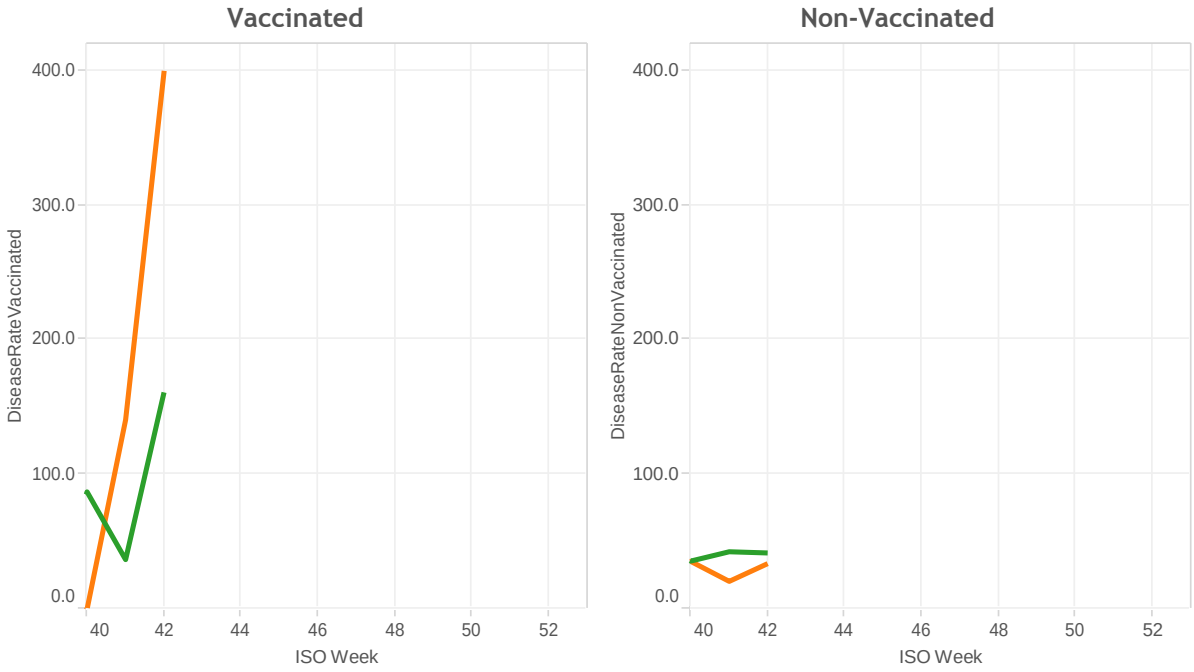


(E) Gastrointestinal by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015

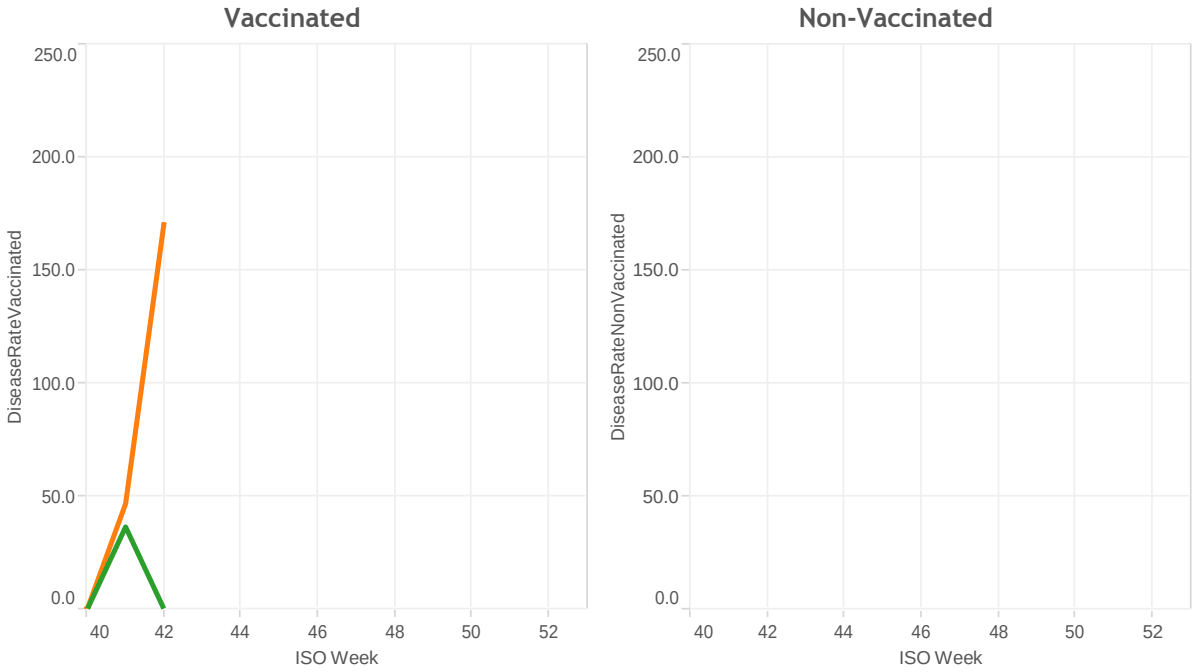


Possible adverse event rates by EMA surveillance condition

(F) General non-specific symptoms by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015

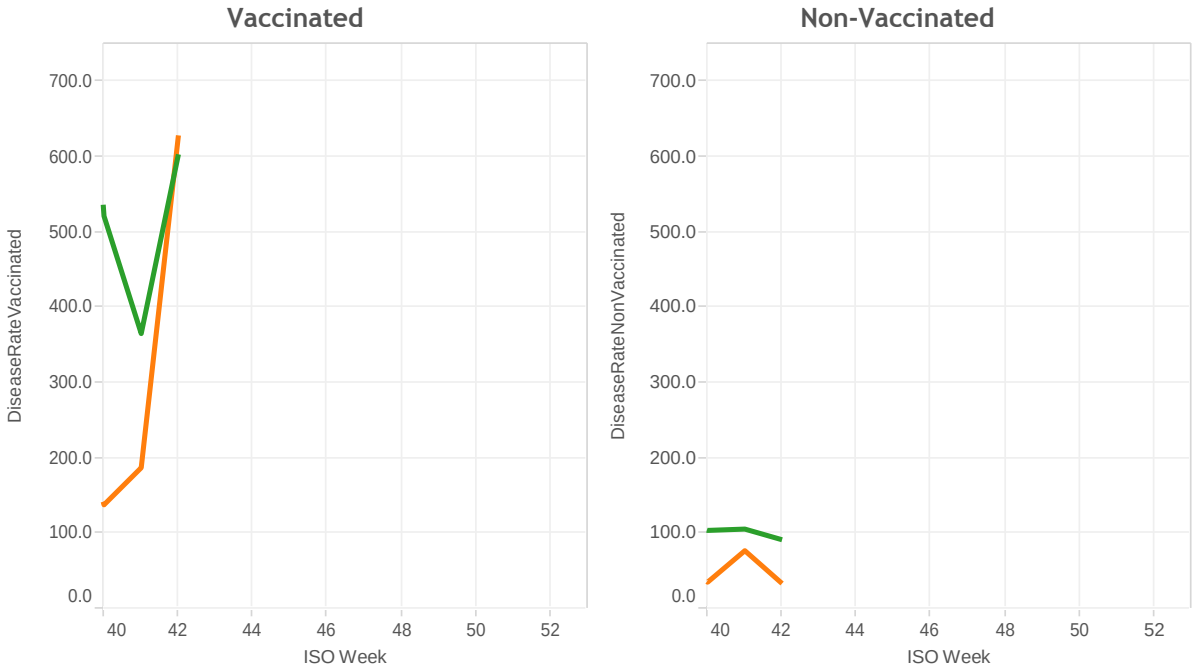


(G) Local symptoms by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015

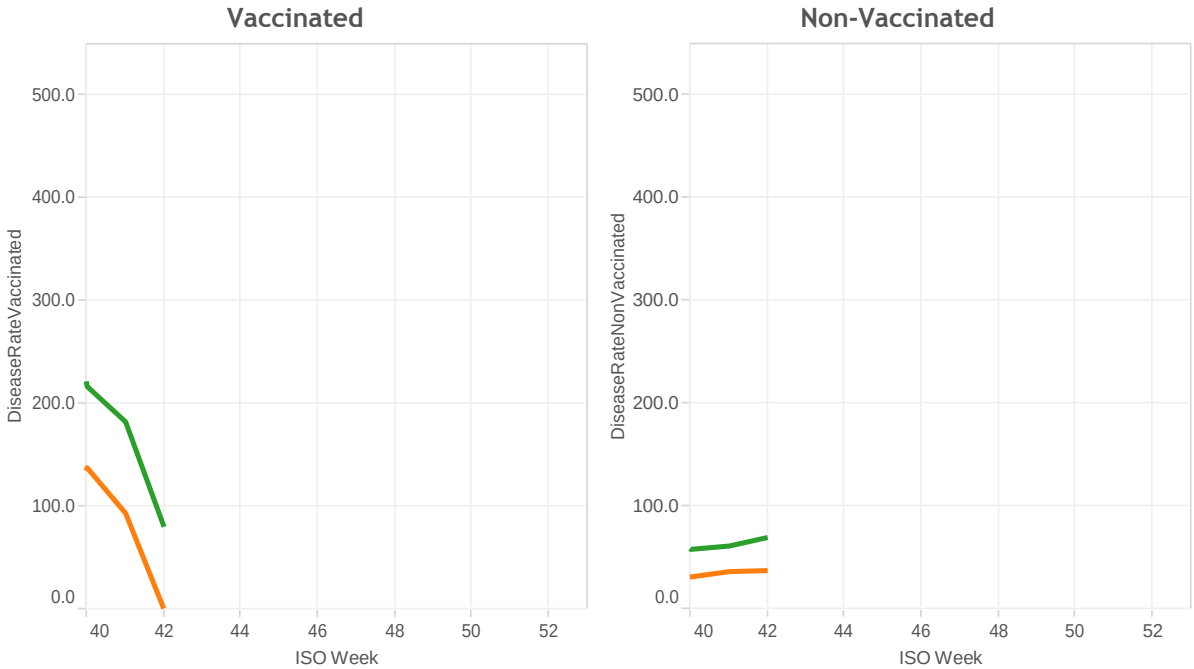


Possible adverse event rates by EMA surveillance condition

(H) Musculoskeletal by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015

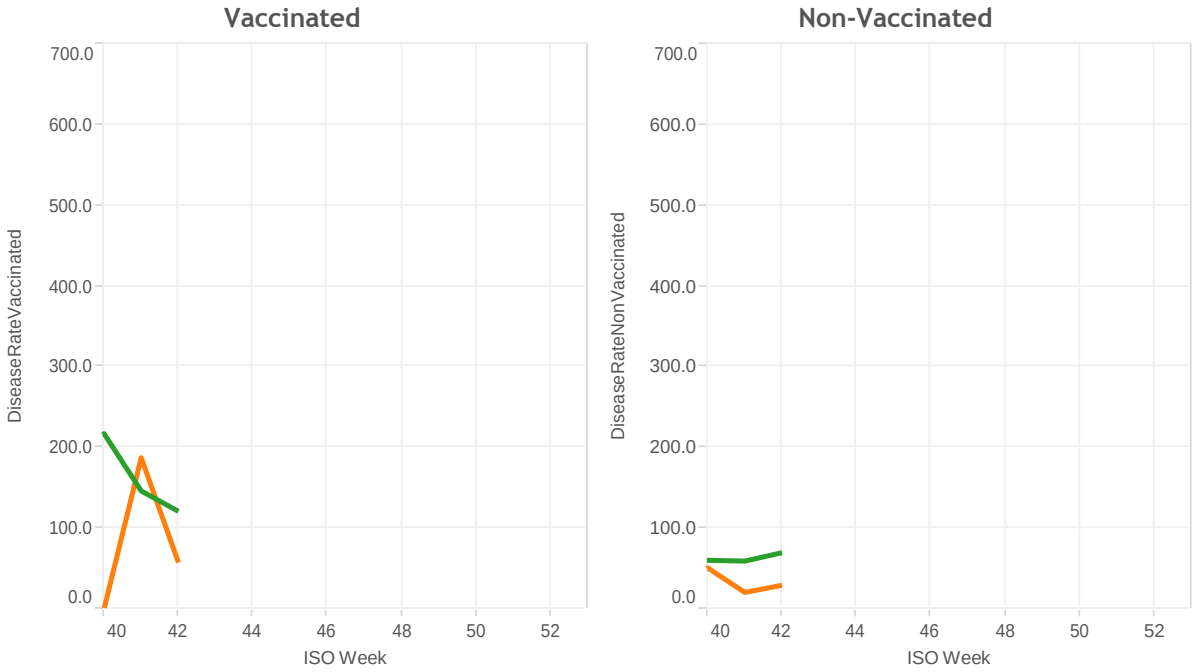


(I) Neurological by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015

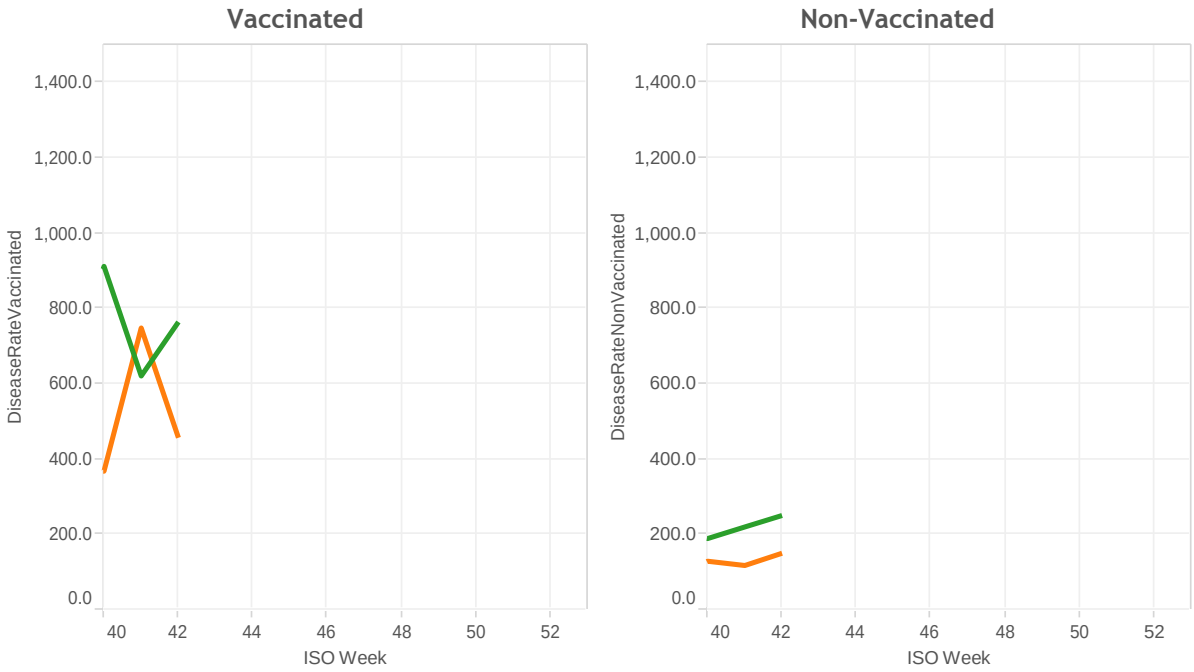


Possible adverse event rates by EMA surveillance condition

(J) Rash by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015



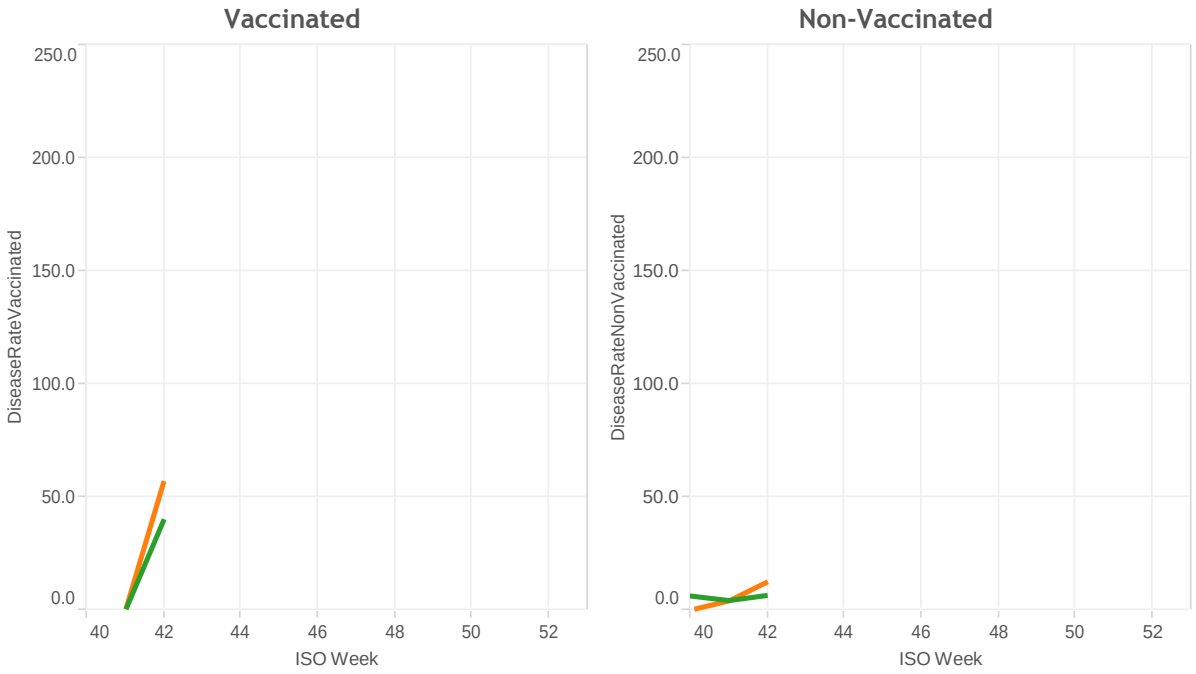
(K) Respiratory/Miscellaneous by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015



Possible adverse event rates by EMA surveillance condition, and weekly summary by vaccine brand

EHR data mining Enhanced passive

(L) Sensitivity/Anaphylaxis by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015



(M) Possible adverse events by GSK or non-GSK vaccines: Incidence rates per 100,000, 2015 **

		Week number 42	41	40	39	38
		Week beginning 12/10/2015	05/10/2015	28/09/2015	21/09/2015	14/09/2015
		Week ending 18/10/2015	11/10/2015	04/10/2015	27/09/2015	20/09/2015
Fever/Pyrexia	GSK	513.5	742.3	231.5	120.8	0.0
	Non-GSK	318.2	279.8	249.2	349.2	1,401.9
Gastrointestinal	GSK	0.0	212.1	0.0	0.0	0.0
	Non-GSK	318.2	101.7	83.1	139.7	0.0
General symptoms	GSK	385.1	212.1	0.0	120.8	0.0
	Non-GSK	231.4	50.9	55.4	0.0	0.0
Local symptoms	GSK	256.7	106.0	0.0	120.8	0.0
	Non-GSK	28.9	25.4	0.0	0.0	0.0
Musculoskeletal	GSK	1,412.1	424.2	347.2	603.9	0.0
	Non-GSK	433.9	254.3	332.2	558.7	467.3
Neurological	GSK	0.0	106.0	347.2	0.0	215.1
	Non-GSK	57.9	152.6	138.4	209.5	467.3
Rash	GSK	128.4	424.2	0.0	120.8	0.0
	Non-GSK	86.8	101.7	138.4	69.8	467.3
Respiratory/Miscellaneous	GSK	641.8	1,166.5	925.9	724.6	215.1
	Non-GSK	636.4	559.5	581.4	279.3	467.3
Sensitivity/Anaphylaxis	GSK	128.4	0.0	0.0	0.0	0.0
	Non-GSK	28.9	0.0	0.0	0.0	467.3
		0.0 200.0 400.0	0.0 200.0 400.0	0.0 200.0 400.0	0.0 200.0 400.0	0.0 200.0 400.0

** It must be noted that the two GSK practices are both conducting enhanced passive surveillance.

Weekly summary of possible adverse event rates by EMA surveillance condition and practice type

(N) Possible adverse events by Enhanced passive or EHR data mining practices: Incidence rates per 100,000 and count of episodes, 2015

Week number		42		41		40		39		38	
Week beginning		12/10/2015		05/10/2015		28/09/2015		21/09/2015		14/09/2015	
Week ending		18/10/2015		11/10/2015		04/10/2015		27/09/2015		20/09/2015	
		Episodes	Rate	Episodes	Rate	Episodes	Rate	Episodes	Rate	Episodes	Rate
Fever/Pyrexia	EHR data mining	10	402.3	11	401.8	8	347.5	5	739.6	3	2,500.0
	Enhanced passive	5	285.7	7	327.6	3	138.0	1	63.1	0	0.0
Gastrointestinal	EHR data mining	10	402.3	4	146.1	3	130.3	1	147.9	0	0.0
	Enhanced passive	1	57.1	2	93.6	0	0.0	1	63.1	0	0.0
General symptoms	EHR data mining	4	160.9	1	36.5	2	86.9	0	0.0	0	0.0
	Enhanced passive	7	400.0	3	140.4	0	0.0	1	63.1	0	0.0
Local symptoms	EHR data mining	0	0.0	1	36.5	0	0.0	0	0.0	0	0.0
	Enhanced passive	3	171.4	1	46.8	0	0.0	1	63.1	0	0.0
Musculoskeletal	EHR data mining	15	603.4	10	365.2	12	521.3	8	1,183.4	1	833.3
	Enhanced passive	11	628.6	4	187.2	3	138.0	5	315.7	0	0.0
Neurological	EHR data mining	2	80.5	5	182.6	5	217.2	3	443.8	0	0.0
	Enhanced passive	0	0.0	2	93.6	3	138.0	0	0.0	2	357.8
Rash	EHR data mining	3	120.7	4	146.1	5	217.2	1	147.9	1	833.3
	Enhanced passive	1	57.1	4	187.2	0	0.0	1	63.1	0	0.0
Respiratory/ Miscellaneous	EHR data mining	19	764.3	17	620.9	21	912.3	4	591.7	1	833.3
	Enhanced passive	8	457.1	16	748.7	8	368.0	6	378.8	1	178.9
Sensitivity/ Anaphylaxis	EHR data mining	1	40.2	0	0.0	0	0.0	0	0.0	1	833.3
	Enhanced passive	1	57.1	0	0.0	0	0.0	0	0.0	0	0.0

Registered Patients	EHR data mining	50,794	50,665	50,548	50,285	50,129
	Enhanced passive	28,419	28,372	28,315	28,236	28,190
Vaccinated Patients	EHR data mining	4,911	3,414	2,422	676	120
	Enhanced passive	4,486	3,725	2,734	1,586	560
Registered Patients	**Total**	80,727	80,720	80,582	80,251	80,195
Vaccinated Patients	**Total**	9,397	7,139	5,156	2,262	680

Further information:

Post-authorisation safety surveillance pilot study

The European Medicines Agency (EMA) has set out new requirements for influenza vaccine safety surveillance that all Marketing Authorisation Holders (MAHs) providing vaccines in the EU must address. This pilot, funded by GlaxoSmithKline and conducted by the [redacted] demonstrates the potential of routinely collected data in the UK to provide timely and relevant information on influenza vaccine safety.

We are assessing adverse event of interest (AEI) frequencies among subjects who have received the influenza vaccine, using routinely collected data in nine primary care practices. AEIs up to 14 days from the date of vaccination are included for vaccinated patients. We are also providing the rate of these events in non-vaccinated patients, to assess background rates and trends. Where these conditions are found in non-vaccinated subjects we call them illness-disease episodes (IDE).

Three practices are taking part in the enhanced passive surveillance sub-study, where a reporting card has been given to vaccinated patients to return to the practices.

This report shows the weekly data flow capturing vaccine coverage, and proportions of patients reporting possible AEIs within the EMA's surveillance condition categories. The results of this pilot will be used to assess whether the data collected in the study meet the requirements of enhanced safety surveillance as stipulated in the interim guidance issued by EMA in April 2014.

This pilot study has received [redacted] approval (REF: 15/LO/1254).

How rates of possible adverse events are calculated

Denominator: The vaccinated denominator are all registered patients in the participating practices who have received the seasonal influenza vaccine in the preceding 2 weeks. The non-vaccinated denominator are all registered patients who have not received the seasonal influenza vaccine to date.

Numerator: The numerator for the vaccinated patients is the number of possible adverse events occurring during the current study week, which happened within a 14-day window after the patient received the seasonal influenza vaccine. The numerator for the non-vaccinated patients is the number of possible adverse events occurring during the study week, for non-vaccinated patients.

Detailed numerators and denominators for the vaccinated patients are stated in graph (L), page 8.

Vaccinated and non-vaccinated comparisons

This pilot study is not designed to provide a formal comparison of the two groups, but the rates of possible AEIs in the non-vaccinated population are included to provide a crude background rate. In future years, once more data has been collected, a more accurate background rate could be established using a 5 year average.

Timeliness of the data

In routine primary care data, the date of recording may differ from the date of the event. Sometimes GPs may add an entry to the patient's record several weeks after the date of the event. Usually, this lag in recording would not be greater than 6 weeks. Therefore, it is expected that each week there may be a small variation in the AEI rates from previous weeks, as new data is recorded.

Further information:

Data extraction process and information governance

Data are extracted twice weekly from practice systems by Apollo Medical Systems on behalf of the [redacted] Patients who have withheld consent for data sharing are excluded from the extraction process. Data are pseudonymised as close to source as possible.

Data are held on secure servers at the Section of Clinical Medicine and Ageing at the [redacted] Both Apollo and the [redacted] are registered and compliant with the Data Protection Act and fully compliant with all relevant HSCIC and NHS data information governance best practice.

For further information, please contact:

Professor [redacted]
[redacted]

[redacted]

[redacted]

Post-authorisation safety study of influenza vaccine

Key Statistics:

Week Number/Year…….43/2015
Week Starting - Ending……..19/10/2015 - 25/10/2015
No. of Practices……9
Population…….80796 (10854 vaccinated)

Post-authorisation safety study:

The European Medicines Agency (EMA) has set out new requirements for influenza vaccine safety surveillance that all Marketing Authorisation Holders (MAHs) providing vaccines in the EU must address. This pilot, funded by Glaxo-SmithKline and conducted by the [redacted] explores the use of routinely collected data in the UK to provide timely and relevant information on influenza vaccine safety.

UK primary care is highly computerised, though the major suppliers have different data models, coding systems, and methods of data access. This pilot study demonstrates the feasibility of drawing together the heterogeneous data from different brands of computer system into a single report format.

Key messages:

Vaccine exposure:

Vaccine exposure rates for all ages have **increased** from **11.86 in week 42** to **13.67 in week 43**.

Practice types:
Enhanced passive practices gave vaccinated patients a card to prompt reporting; Electronic Health Record (EHR) data mining practices have findings reported from routine data.

Possible adverse events in the vaccinated population by Enhanced passive and EHR data mining practices (per 100,000 patients):

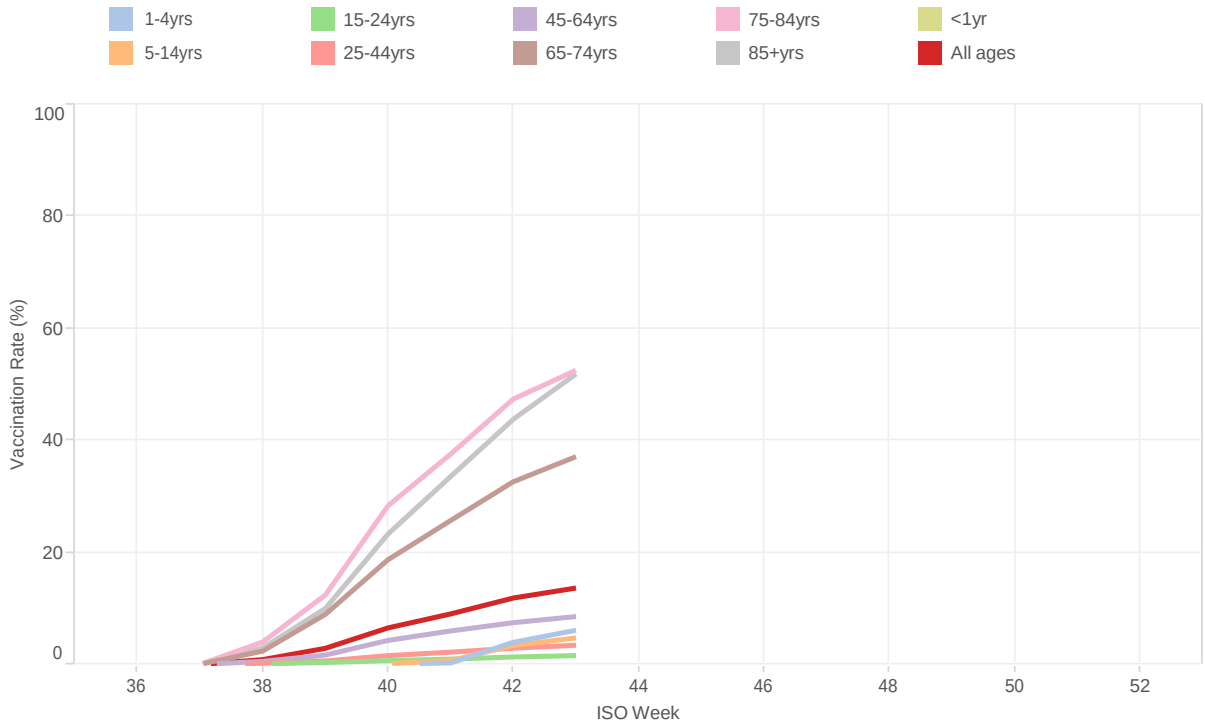
· **Fever/Pyrexia :** Enhanced passive rate was **285.7** in week 42 compared with **647.0** in week 43. EHR data mining rate was **402.3** in week 42 compared with **432.9** in week 43.
· **Gastrointestinal :** Enhanced passive rate was **57.1** in week 42 compared with **71.9** in week 43. EHR data mining rate was **402.3** in week 42 compared with **216.5** in week 43.
· **General symptoms :** Enhanced passive rate was **400.0** in week 42 compared with **215.7** in week 43. EHR data mining rate was **160.9** in week 42 compared with **86.6** in week 43.
· **Local symptoms :** Enhanced passive rate was **171.4** in week 42 compared with **0.0** in week 43. EHR data mining rate was **0.0** in week 42 compared with **0.0** in week 43.
· **Musculoskeletal :** Enhanced passive rate was **628.6** in week 42 compared with **143.8** in week 43. EHR data mining rate was **603.4** in week 42 compared with **432.9** in week 43.
· **Neurological :** Enhanced passive rate was **0.0** in week 42 compared with **71.9** in week 43. EHR data mining rate was **80.5** in week 42 compared with **476.2** in week 43.
· **Rash :** Enhanced passive rate was **57.1** in week 42 compared with **0.0** in week 43. EHR data mining rate was **120.7** in week 42 compared with **86.6** in week 43.
· **Respiratory/Miscellaneous :** Enhanced passive rate was **457.1** in week 42 compared with **431.3** in week 43. EHR data mining rate was **764.3** in week 42 compared with **822.5** in week 43.
· **Sensitivity/anaphylaxis :** Enhanced passive rate was **57.1** in week 42 compared with **0.0** in week 43. EHR data mining rate was **40.2** in week 42 compared with **0.0** in week 43.

Comment:

The proportion of the practice population vaccinated continued to increase this week. The most common possible adverse event categories this week were respiratory/miscellaneous, musculoskeletal, neurological, and fever/pyrexia.

Influenza vaccine exposure rates

- **Cumulative vaccine exposure rates: All age groups, 2015 ***



* The vaccination exposure rates are a percentage of all registered patients in the pilot practices.

- **Cumulative vaccine exposure rates: All age groups, by vaccine brand, 2015 ***

	GSK vaccine	Non-GSK vaccine
<1yr		
1-4yrs	0.22	7.26
5-14yrs	0.14	5.72
15-24yrs	1.81	1.55
25-44yrs	3.39	3.44
45-64yrs	9.16	8.41
65-74yrs	42.83	35.56
75-84yrs	61.57	49.81
85+yrs	58.69	49.91
All ages	16.66	12.96

* The GSK vaccine rates are based on the vaccine exposure rates in 2 out of 9 of the pilot practices.

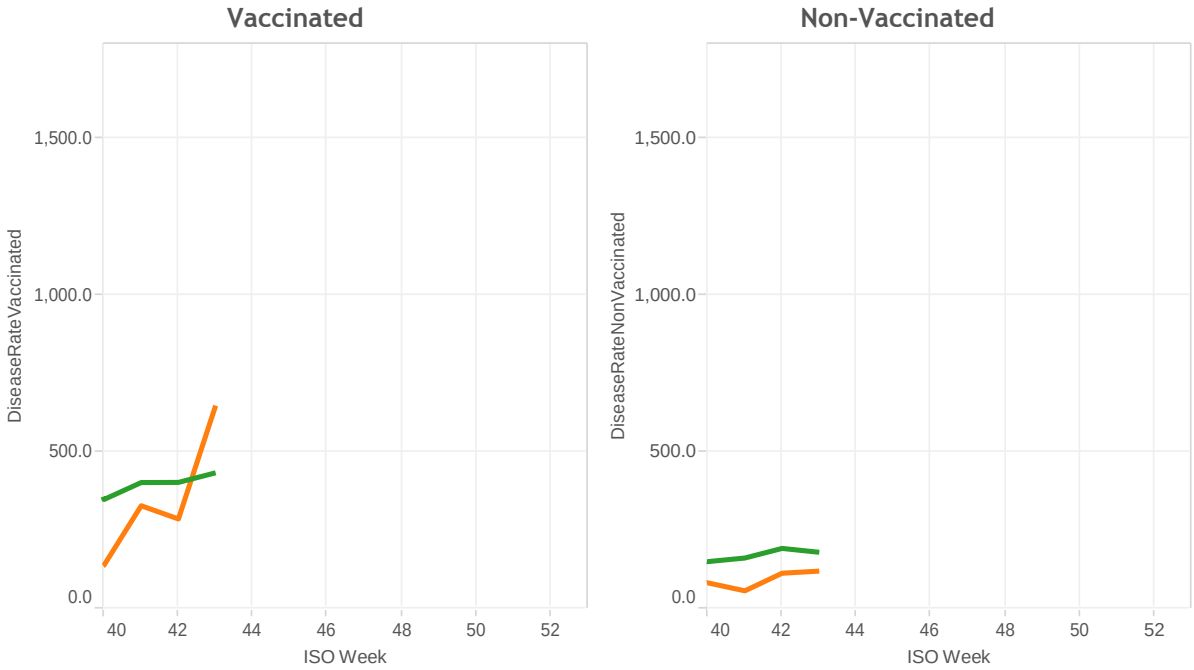
- **Key denominators**

	Registered Patients	Vaccinated Patients	Vaccination Rate
Non-GSK vaccine	64,284	8,333	12.96
GSK vaccine	15,134	2,521	16.66
Grand Total	80,796	10,854	13.67

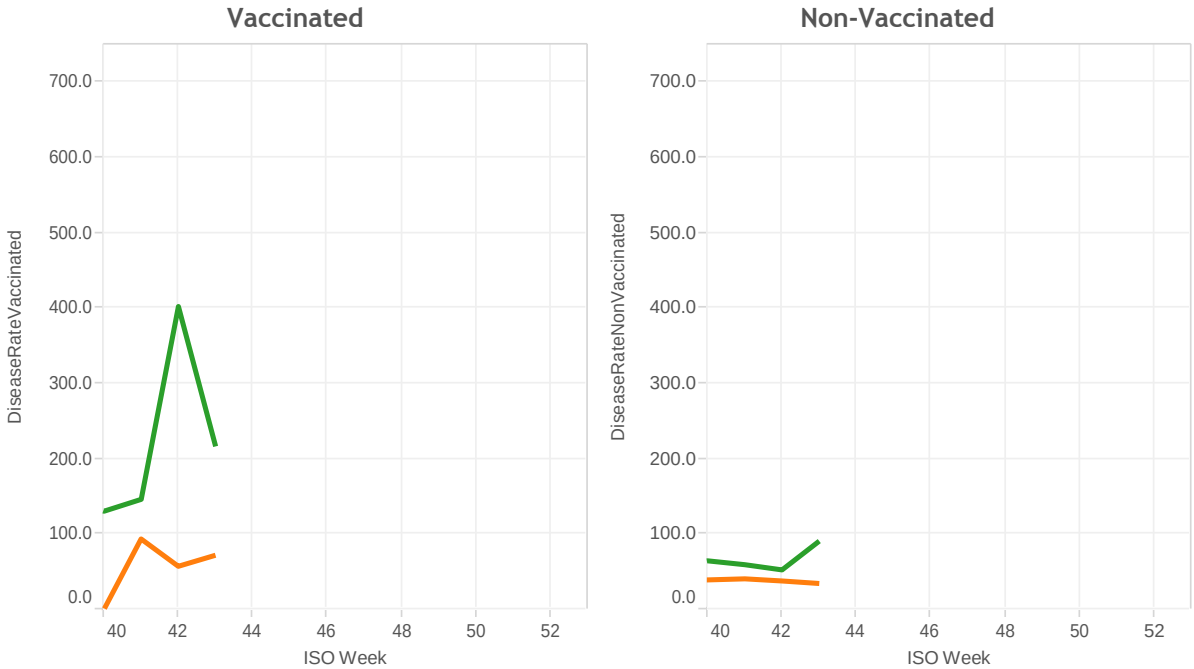
	Registered Patients	Vaccinated Patients	Vaccination Rate
EHR data mining	50,932	5,734	11.26
Enhanced passive	28,486	5,120	17.97
Grand Total	80,796	10,854	13.67

Possible adverse event rates by EMA surveillance condition

- **Fever/Pyrexia by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

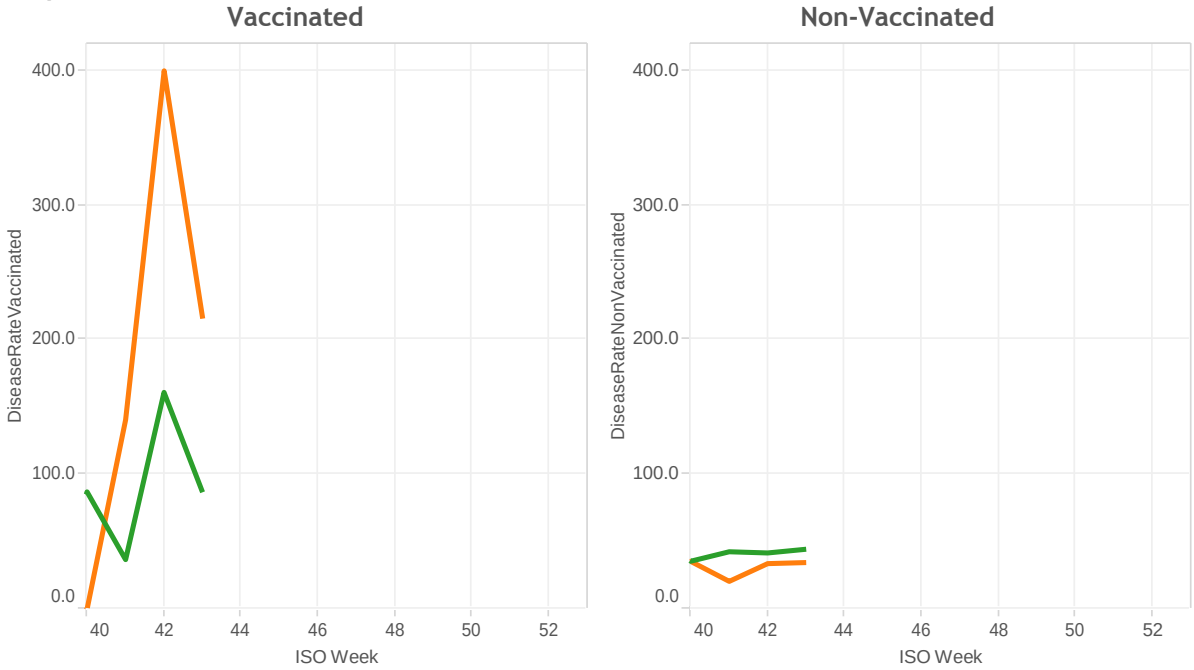


- **Gastrointestinal by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

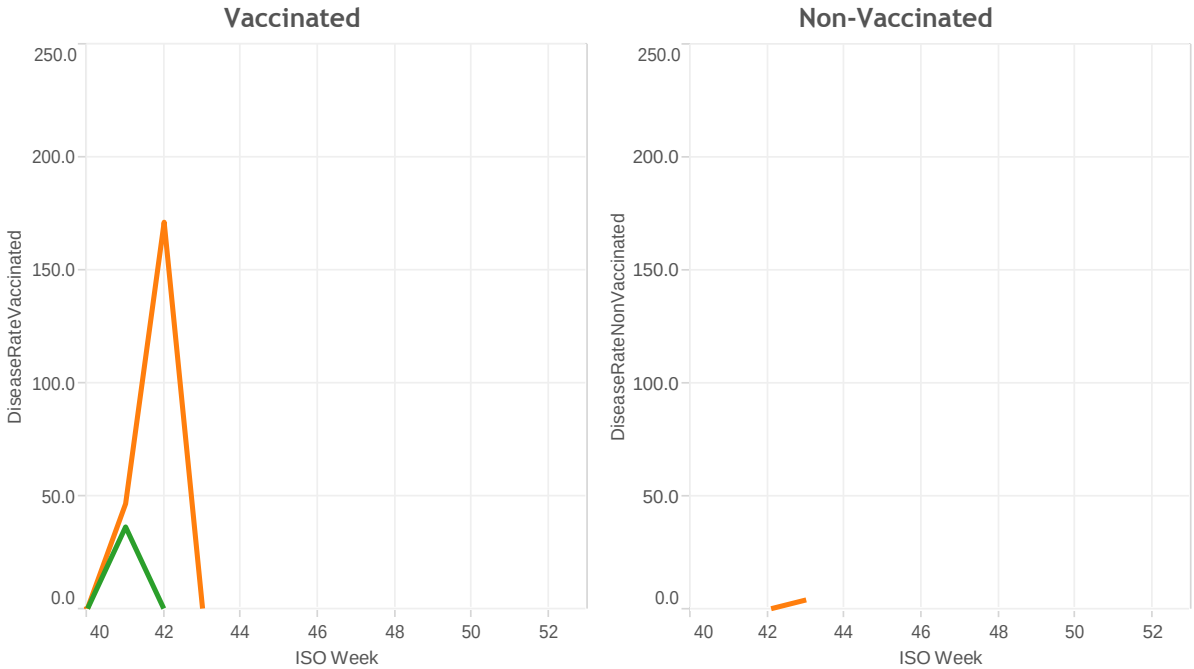


Possible adverse event rates by EMA surveillance condition

- **General non-specific symptoms by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

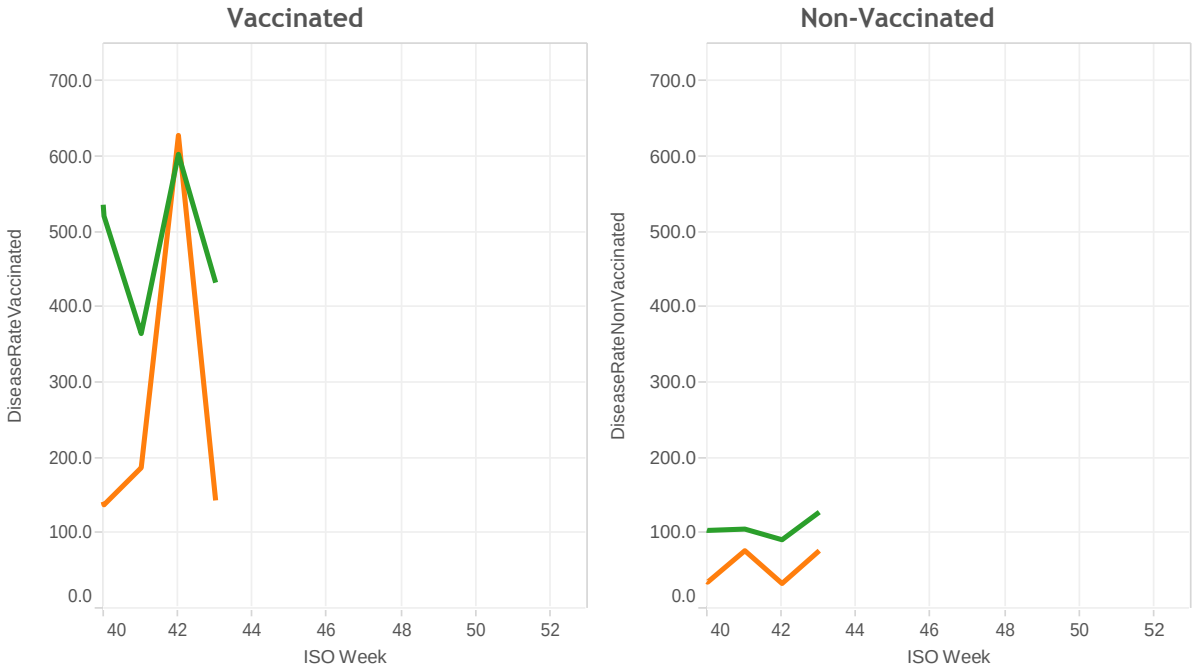


- **Local symptoms by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

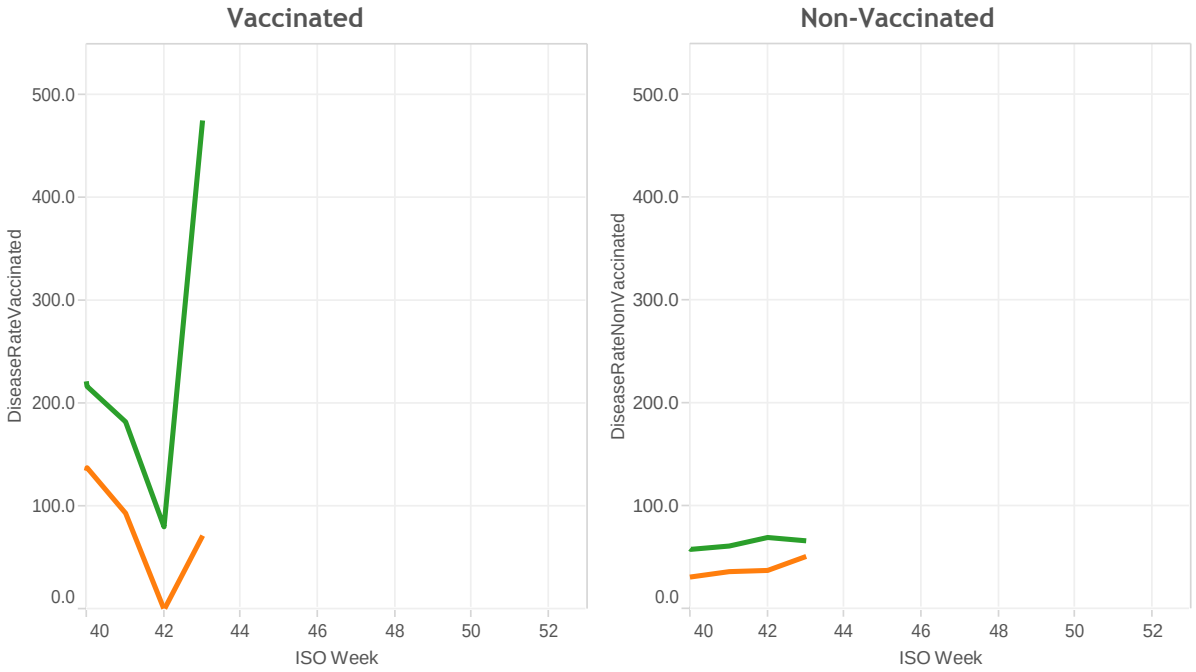


Possible adverse event rates by EMA surveillance condition

- **Musculoskeletal by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

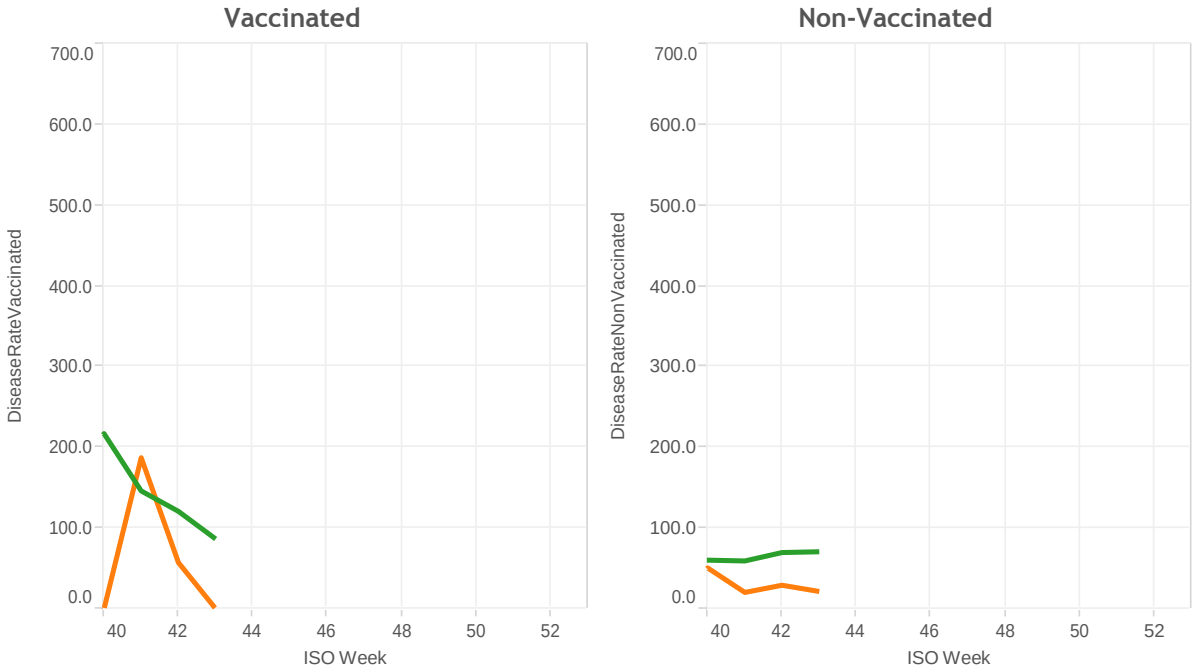


- **Neurological by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

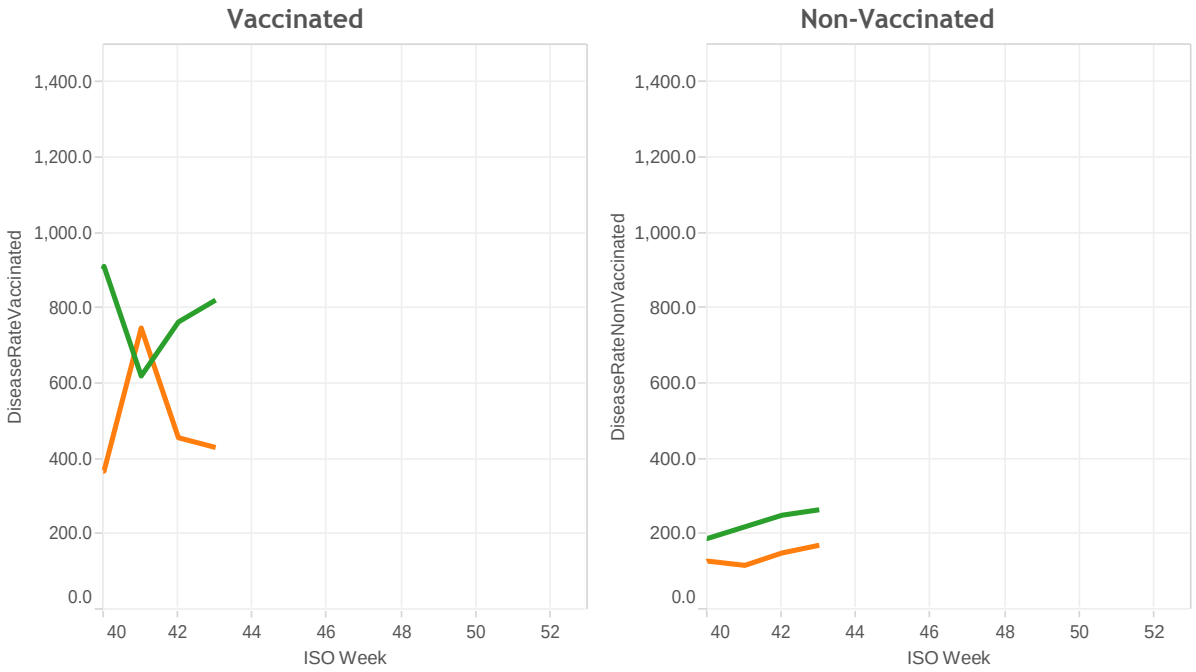


Possible adverse event rates by EMA surveillance condition

- **Rash by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

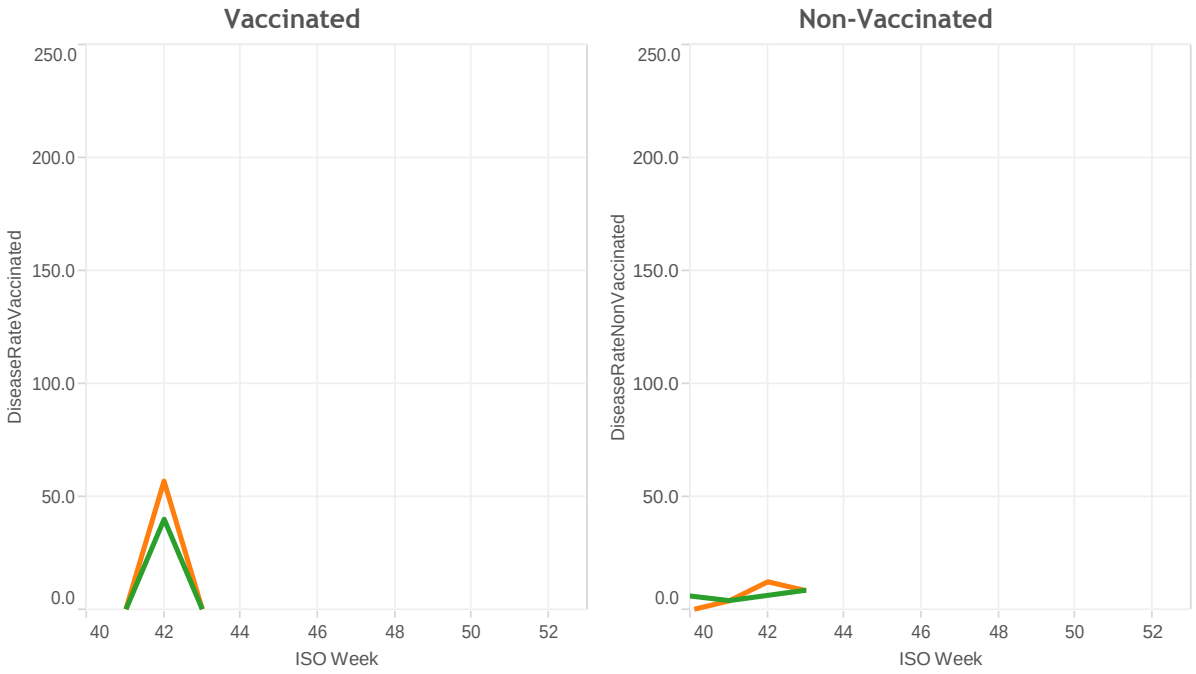


- **Respiratory/Miscellaneous by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

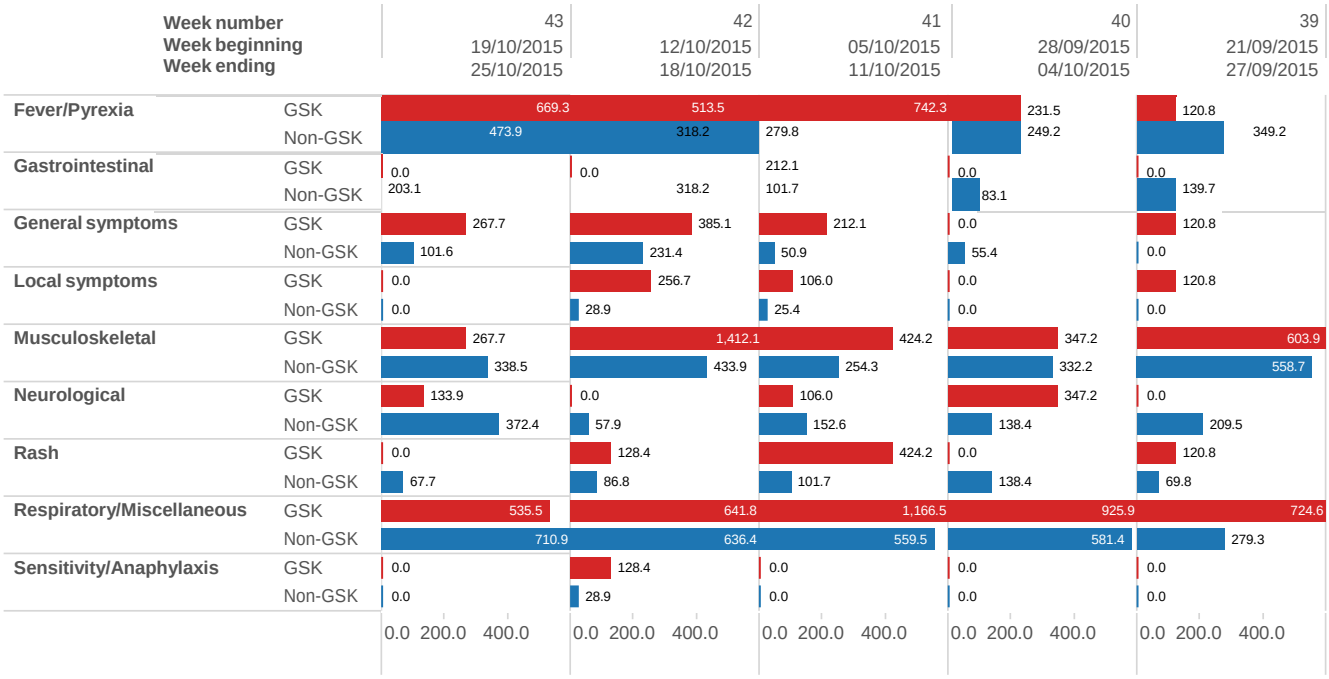


Possible adverse event rates by EMA surveillance condition, and weekly summary by vaccine brand

- **Sensitivity/Anaphylaxis by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**



- **Possible adverse events by GSK or non-GSK vaccines: Incidence rates per 100,000, 2015 ****



** It must be noted that the two GSK practices are both conducting enhanced passive surveillance.

Weekly summary of possible adverse event rates by EMA surveillance condition and practice type

- **Possible adverse events by Enhanced passive or EHR data mining practices: Incidence rates per 100,000 and count of episodes, 2015**

Week number		43		42		41		40		39	
Week beginning		19/10/2015		12/10/2015		05/10/2015		28/09/2015		21/09/2015	
Week ending		25/10/2015		18/10/2015		11/10/2015		04/10/2015		27/09/2015	
		Episodes	Rate	Episodes	Rate	Episodes	Rate	Episodes	Rate	Episodes	Rate
Fever/Pyrexia	EHR data mining	10	432.9	10	402.3	11	401.8	8	347.5	5	739.6
	Enhanced passive	9	647.0	5	285.7	7	327.6	3	138.0	1	63.1
Gastrointestinal	EHR data mining	5	216.5	10	402.3	4	146.1	3	130.3	1	147.9
	Enhanced passive	1	71.9	1	57.1	2	93.6	0	0.0	1	63.1
General symptoms	EHR data mining	2	86.6	4	160.9	1	36.5	2	86.9	0	0.0
	Enhanced passive	3	215.7	7	400.0	3	140.4	0	0.0	1	63.1
Local symptoms	EHR data mining	0	0.0	0	0.0	1	36.5	0	0.0	0	0.0
	Enhanced passive	0	0.0	3	171.4	1	46.8	0	0.0	1	63.1
Musculoskeletal	EHR data mining	10	432.9	15	603.4	10	365.2	12	521.3	8	1,183.4
	Enhanced passive	2	143.8	11	628.6	4	187.2	3	138.0	5	315.7
Neurological	EHR data mining	11	476.2	2	80.5	5	182.6	5	217.2	3	443.8
	Enhanced passive	1	71.9	0	0.0	2	93.6	3	138.0	0	0.0
Rash	EHR data mining	2	86.6	3	120.7	4	146.1	5	217.2	1	147.9
	Enhanced passive	0	0.0	1	57.1	4	187.2	0	0.0	1	63.1
Respiratory/ Miscellaneous	EHR data mining	19	822.5	19	764.3	17	620.9	21	912.3	4	591.7
	Enhanced passive	6	431.3	8	457.1	16	748.7	8	368.0	6	378.8
Sensitivity/ Anaphylaxis	EHR data mining	0	0.0	1	40.2	0	0.0	0	0.0	0	0.0
	Enhanced passive	0	0.0	1	57.1	0	0.0	0	0.0	0	0.0

Registered Patients	EHR data mining	50,932	50,794	50,665	50,548	50,285
	Enhanced passive	28,486	28,419	28,372	28,315	28,236
Vaccinated Patients	EHR data mining	5,734	4,911	3,414	2,422	676
	Enhanced passive	5,120	4,486	3,725	2,734	1,586
Registered Patients	**Total**	80,796	80,727	80,720	80,582	80,251
Vaccinated Patients	**Total**	10,854	9,397	7,139	5,156	2,262

Further information:

Post-authorisation safety surveillance pilot study

The European Medicines Agency (EMA) has set out new requirements for influenza vaccine safety surveillance that all Marketing Authorisation Holders (MAHs) providing vaccines in the EU must address. This pilot, funded by GlaxoSmithKline and conducted by the [redacted] demonstrates the potential of routinely collected data in the UK to provide timely and relevant information on influenza vaccine safety.

We are assessing adverse event of interest (AEI) frequencies among subjects who have received the influenza vaccine, using routinely collected data in nine primary care practices. AEIs up to 14 days from the date of vaccination are included for vaccinated patients. We are also providing the rate of these events in non-vaccinated patients, to assess background rates and trends. Where these conditions are found in non-vaccinated subjects we call them illness-disease episodes (IDE).

Three practices are taking part in the enhanced passive surveillance sub-study, where a reporting card has been given to vaccinated patients to return to the practices.

This report shows the weekly data flow capturing vaccine coverage, and proportions of patients reporting possible AEIs within the EMA's surveillance condition categories. The results of this pilot will be used to assess whether the data collected in the study meet the requirements of enhanced safety surveillance as stipulated in the interim guidance issued by EMA in April 2014.

This pilot study has received [redacted] approval (REF: 15/LO/1254).

How rates of possible adverse events are calculated

Denominator: The vaccinated denominator are all registered patients in the participating practices who have received the seasonal influenza vaccine in the preceding 2 weeks. The non-vaccinated denominator are all registered patients who have not received the seasonal influenza vaccine to date.

Numerator: The numerator for the vaccinated patients is the number of possible adverse events occurring during the current study week, which happened within a 14-day window after the patient received the seasonal influenza vaccine. The numerator for the non-vaccinated patients is the number of possible adverse events occurring during the study week, for non-vaccinated patients.

Detailed numerators and denominators for the vaccinated patients are stated in graph (L), page 8.

Vaccinated and non-vaccinated comparisons

This pilot study is not designed to provide a formal comparison of the two groups, but the rates of possible AEIs in the non-vaccinated population are included to provide a crude background rate. In future years, once more data has been collected, a more accurate background rate could be established using a 5 year average.

Timeliness of the data

In routine primary care data, the date of recording may differ from the date of the event. Sometimes GPs may add an entry to the patient's record several weeks after the date of the event. Usually, this lag in recording would not be greater than 6 weeks. Therefore, it is expected that each week there may be a small variation in the AEI rates from previous weeks, as new data is recorded.

Further information:

Data extraction process and information governance

Data are extracted twice weekly from practice systems by Apollo Medical Systems on behalf of the [redacted] Patients who have withheld consent for data sharing are excluded from the extraction process. Data are pseudonymised as close to source as possible.

Data are held on secure servers at the Section of Clinical Medicine and Ageing at the [redacted] Both Apollo and the [redacted] are registered and compliant with the Data Protection Act and fully compliant with all relevant HSCIC and NHS data information governance best practice.

For further information, please contact:

Professor [redacted]
[redacted]
[redacted]

[redacted]

Post-authorisation safety study of influenza vaccine

Key Statistics:

Week Number/Year…….44/2015
Week Starting - Ending……..…26/10/2015 - 01/11/2015
No. of Practices……9
Population…….80831 (11845 vaccinated)

Post-authorisation safety study:

The European Medicines Agency (EMA) has set out new requirements for influenza vaccine safety surveillance that all Marketing Authorisation Holders (MAHs) providing vaccines in the EU must address. This pilot, funded by Glaxo-SmithKline and conducted by the [redacted] explores the use of routinely collected data in the UK to provide timely and relevant information on influenza vaccine safety.

UK primary care is highly computerised, though the major suppliers have different data models, coding systems, and methods of data access. This pilot study demonstrates the feasibility of drawing together the heterogeneous data from different brands of computer system into a single report format.

Key messages:

Vaccine exposure:

Vaccine exposure rates for all ages have **increased** from **13.67 in week 43** to **14.89 in week 44**.

Practice types:
Enhanced passive practices gave vaccinated patients a card to prompt reporting; Electronic Health Record (EHR) data mining practices have findings reported from routine data.

Possible adverse events in the vaccinated population by Enhanced passive and EHR data mining practices (per 100,000 patients):

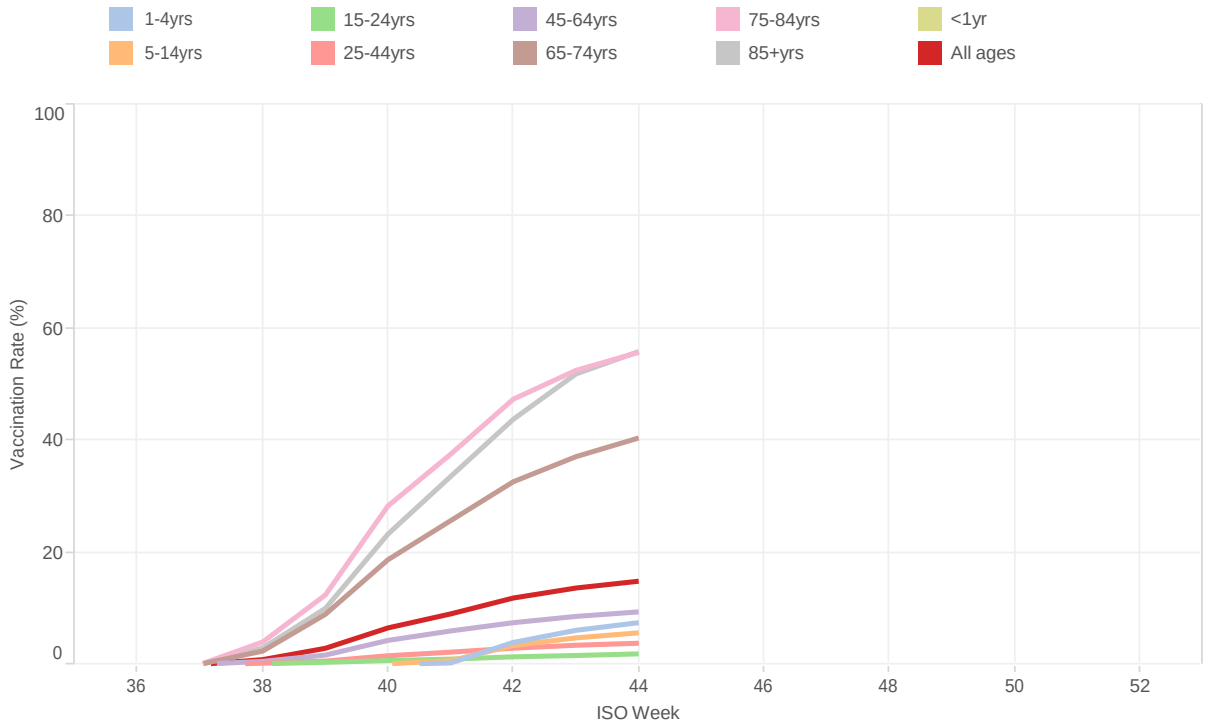
- **Fever/Pyrexia :** Enhanced passive rate was **647.0** in week 43 compared with **182.8** in week 44. EHR data mining rate was **432.9** in week 43 compared with **1273.4** in week 44.
- **Gastrointestinal :** Enhanced passive rate was **71.9** in week 43 compared with **0.0** in week 44. EHR data mining rate was **216.5** in week 43 compared with **374.5** in week 44.
- **General symptoms :** Enhanced passive rate was **215.7** in week 43 compared with **91.4** in week 44. EHR data mining rate was **86.6** in week 43 compared with **299.6** in week 44.
- **Local symptoms :** Enhanced passive rate was **0.0** in week 43 compared with **91.4** in week 44. EHR data mining rate was **0.0** in week 43 compared with **0.0** in week 44.
- **Musculoskeletal :** Enhanced passive rate was **143.8** in week 43 compared with **274.2** in week 44. EHR data mining rate was **432.9** in week 43 compared with **524.3** in week 44.
- **Neurological :** Enhanced passive rate was **71.9** in week 43 compared with **0.0** in week 44. EHR data mining rate was **476.2** in week 43 compared with **299.6** in week 44.
- **Rash :** Enhanced passive rate was **0.0** in week 43 compared with **0.0** in week 44. EHR data mining rate was **86.6** in week 43 compared with **149.8** in week 44.
- **Respiratory/Miscellaneous :** Enhanced passive rate was **431.3** in week 43 compared with **182.8** in week 44. EHR data mining rate was **822.5** in week 43 compared with **1498.1** in week 44.
- **Sensitivity/anaphylaxis :** Enhanced passive rate was **0.0** in week 43 compared with **0.0** in week 44. EHR data mining rate was **0.0** in week 43 compared with **74.9** in week 44.

Comment:

The proportion of the practice population vaccinated continued to increase this week. The most common possible adverse event categories this week were respiratory/miscellaneous, and fever/pyrexia.

Influenza vaccine exposure rates

- **Cumulative vaccine exposure rates: All age groups, 2015 ***



* The vaccination exposure rates are a percentage of all registered patients in the pilot practices.

- **Cumulative vaccine exposure rates: All age groups, by vaccine brand, 2015 ***

	GSK vaccine	Non-GSK vaccine
<1yr		
1-4yrs	1.34	8.67
5-14yrs	0.43	6.78
15-24yrs	1.98	1.86
25-44yrs	3.73	3.82
45-64yrs	10.24	9.17
65-74yrs	47.54	38.53
75-84yrs	67.53	52.21
85+yrs	62.36	54.01
All ages	18.35	14.07

* The GSK vaccine rates are based on the vaccine exposure rates in 2 out of 9 of the pilot practices.

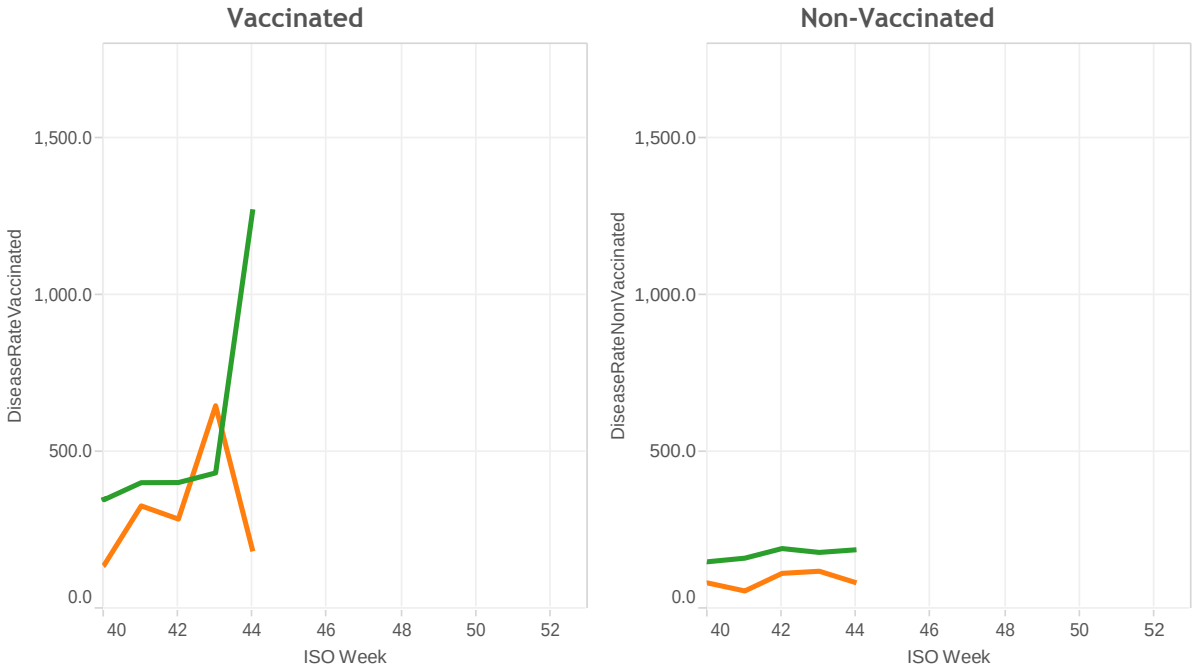
- **Key denominators**

	Registered Patients	Vaccinated Patients	Vaccination Rate
Non-GSK vaccine	64,413	9,063	14.07
GSK vaccine	15,161	2,782	18.35
Grand Total	80,831	11,845	14.89

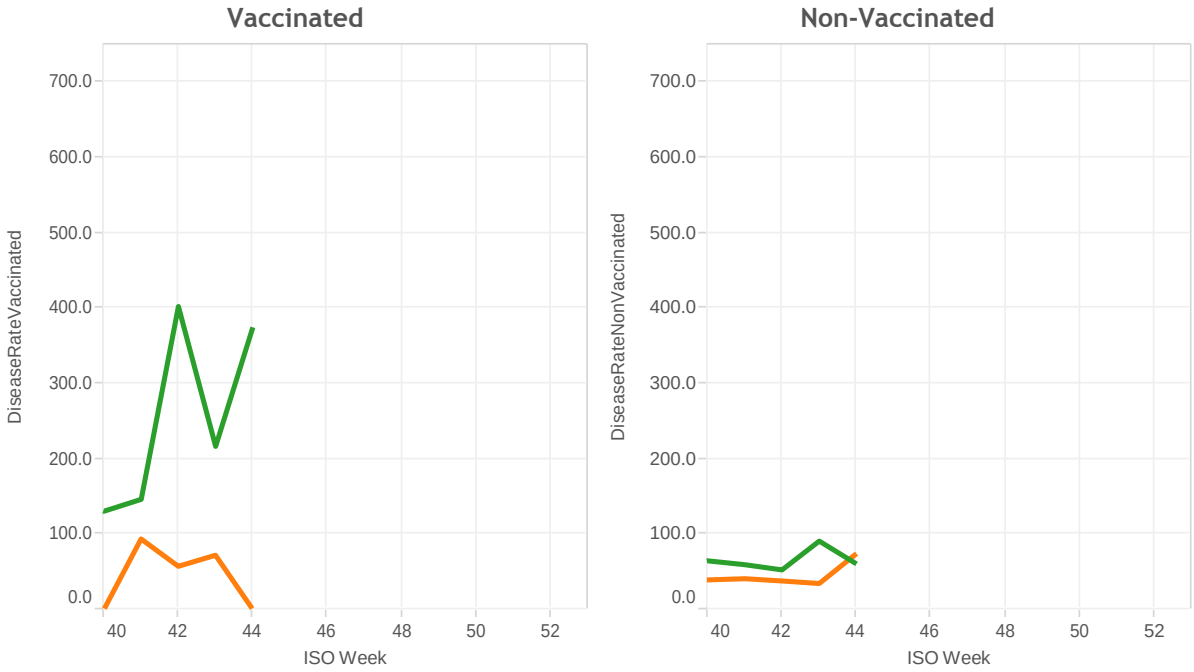
	Registered Patients	Vaccinated Patients	Vaccination Rate
EHR data mining	51,023	6,262	12.27
Enhanced passive	28,551	5,583	19.55
Grand Total	80,831	11,845	14.89

Possible adverse event rates by EMA surveillance condition

- **Fever/Pyrexia by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

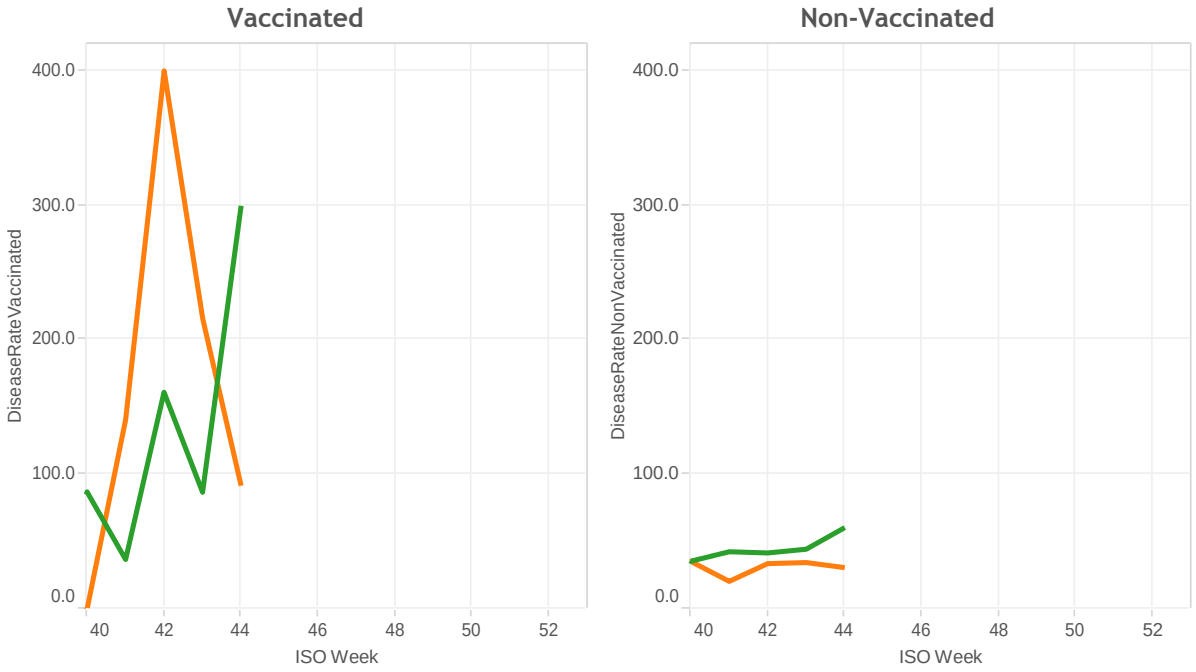


- **Gastrointestinal by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

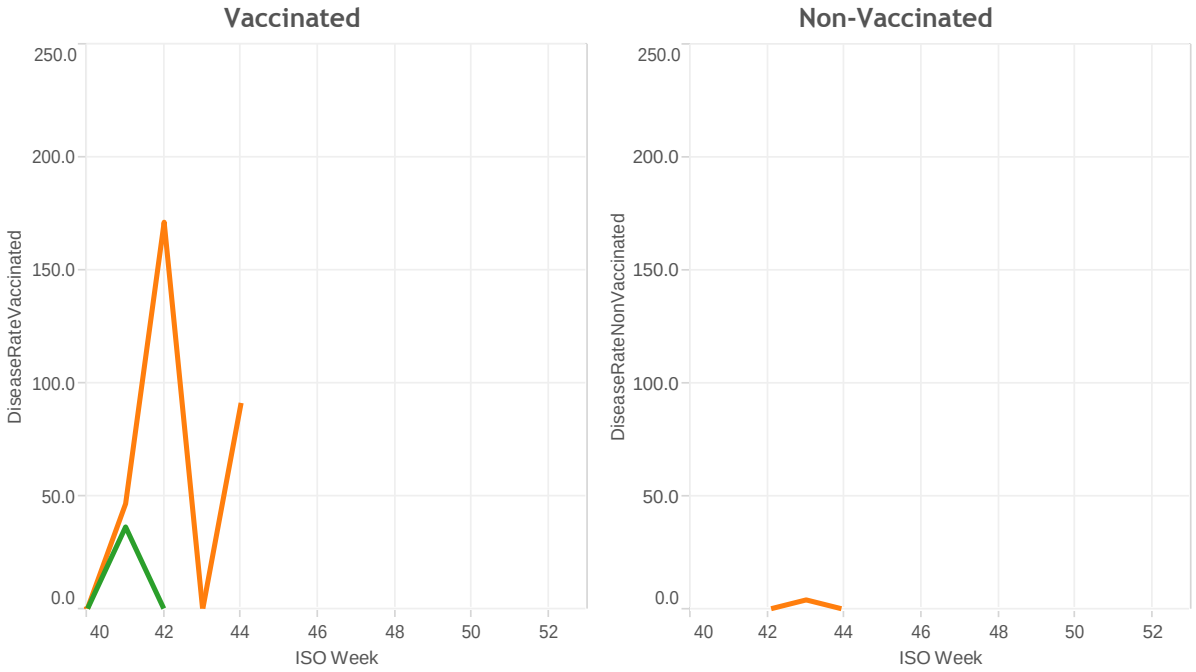


Possible adverse event rates by EMA surveillance condition

- **General non-specific symptoms by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

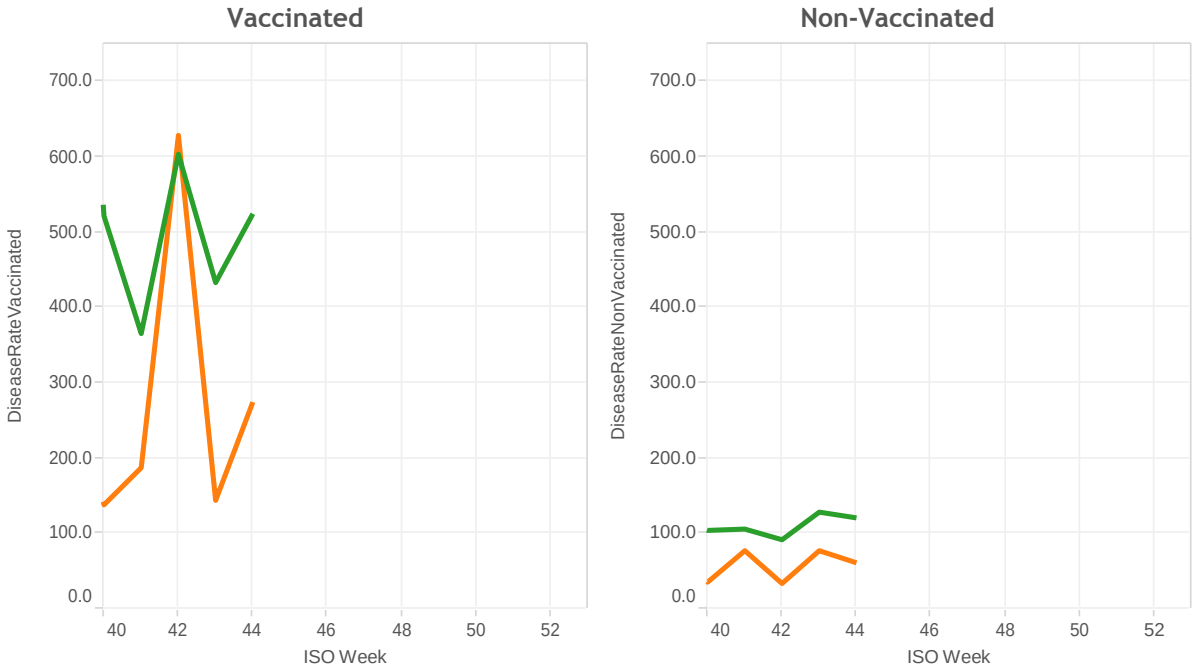


- **Local symptoms by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

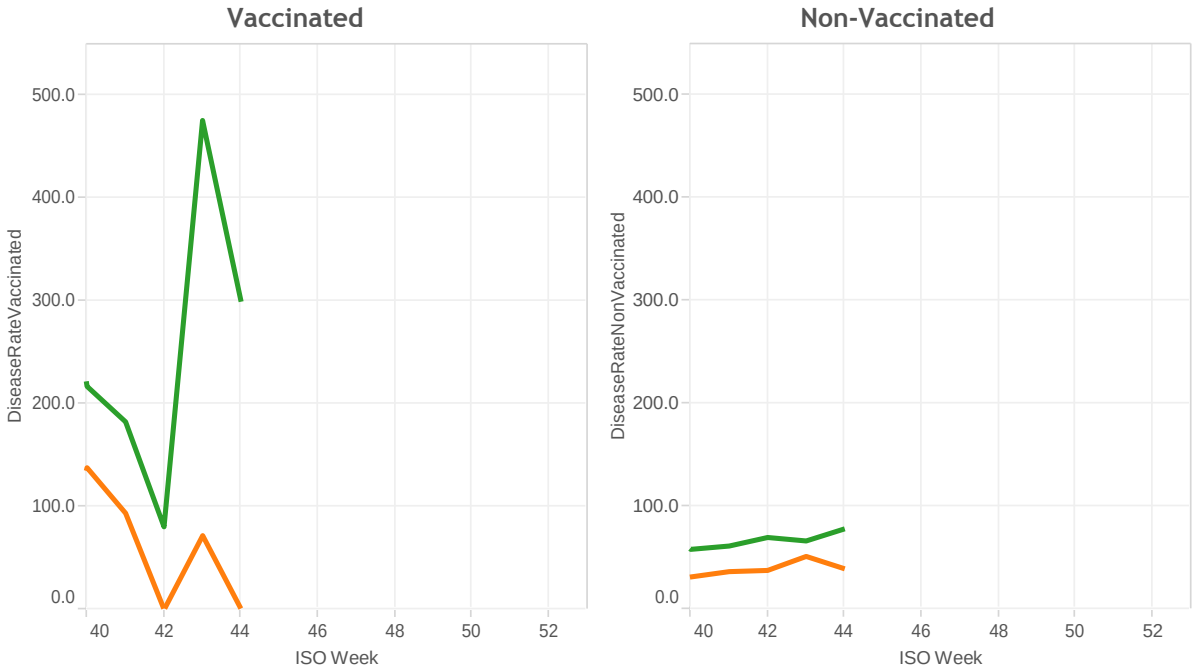


Possible adverse event rates by EMA surveillance condition

- **Musculoskeletal by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

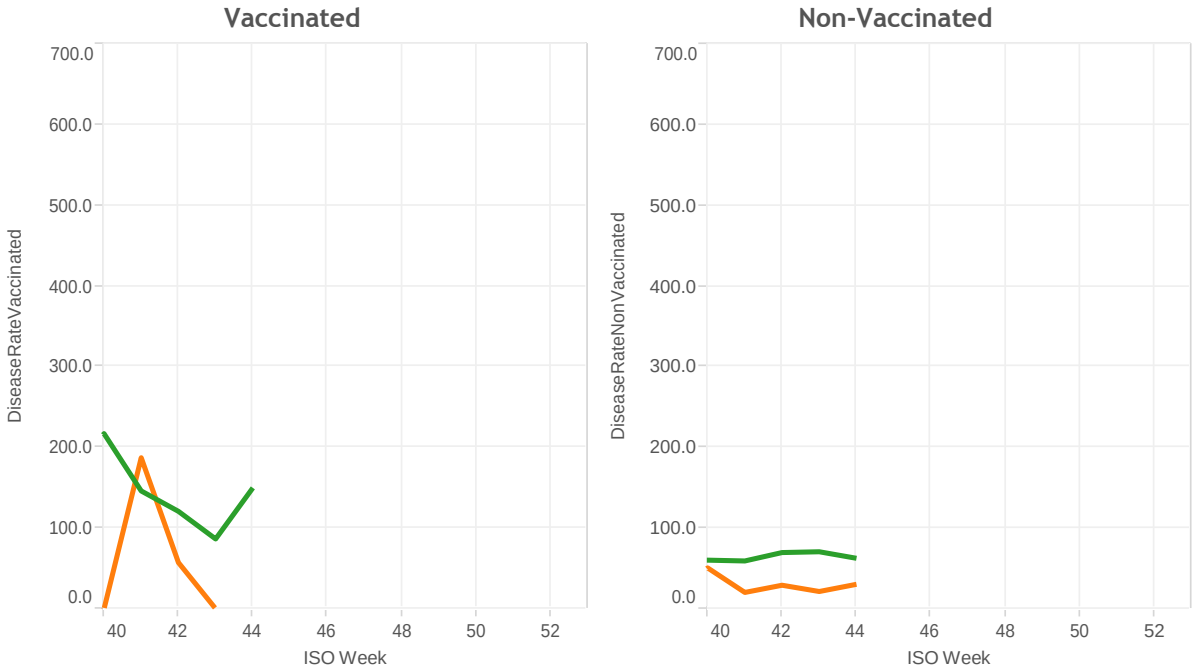


- **Neurological by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

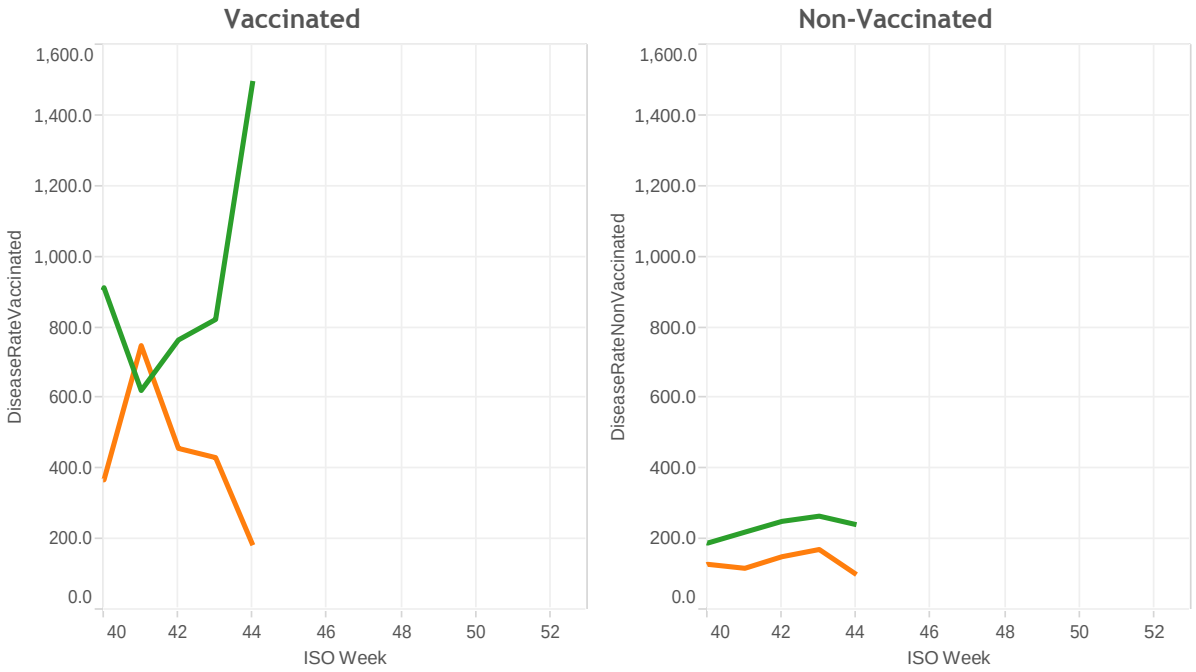


Possible adverse event rates by EMA surveillance condition

- **Rash by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

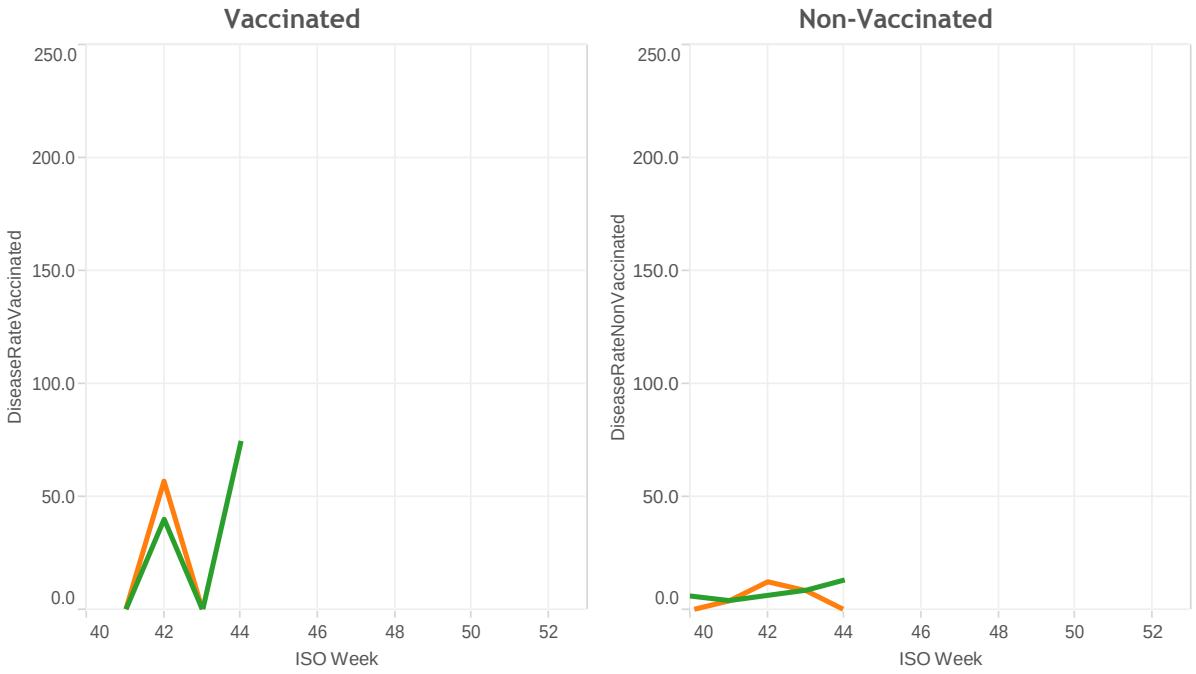


- **Respiratory/Miscellaneous by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

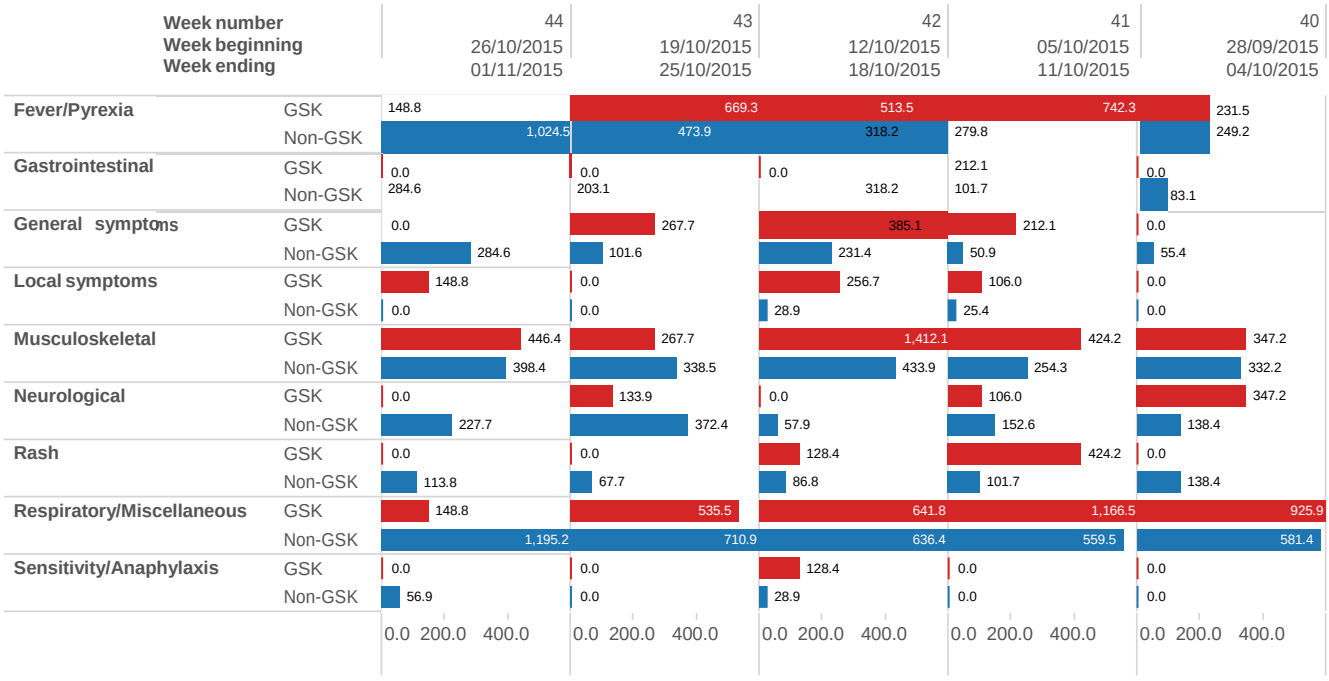


Possible adverse event rates by EMA surveillance condition, and weekly summary by vaccine brand

- **Sensitivity/Anaphylaxis by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**



- **Possible adverse events by GSK or non-GSK vaccines: Incidence rates per 100,000, 2015 ****



** It must be noted that the two GSK practices are both conducting enhanced passive surveillance.

Weekly summary of possible adverse event rates by EMA surveillance condition and practice type

- **Possible adverse events by Enhanced passive or EHR data mining practices: Incidence rates per 100,000 and count of episodes, 2015**

Week number		44		43		42		41		40	
Week beginning		26/10/2015		19/10/2015		12/10/2015		05/10/2015		28/09/2015	
Week ending		01/11/2015		25/10/2015		18/10/2015		11/10/2015		04/10/2015	
		Episodes	Rate	Episodes	Rate	Episodes	Rate	Episodes	Rate	Episodes	Rate
Fever/Pyrexia	EHR data mining	17	1,273.4	10	432.9	10	402.3	11	401.8	8	347.5
	Enhanced passive	2	182.8	9	647.0	5	285.7	7	327.6	3	138.0
Gastrointestinal	EHR data mining	5	374.5	5	216.5	10	402.3	4	146.1	3	130.3
	Enhanced passive	0	0.0	1	71.9	1	57.1	2	93.6	0	0.0
General symptoms	EHR data mining	4	299.6	2	86.6	4	160.9	1	36.5	2	86.9
	Enhanced passive	1	91.4	3	215.7	7	400.0	3	140.4	0	0.0
Local symptoms	EHR data mining	0	0.0	0	0.0	0	0.0	1	36.5	0	0.0
	Enhanced passive	1	91.4	0	0.0	3	171.4	1	46.8	0	0.0
Musculoskeletal	EHR data mining	7	524.3	10	432.9	15	603.4	10	365.2	12	521.3
	Enhanced passive	3	274.2	2	143.8	11	628.6	4	187.2	3	138.0
Neurological	EHR data mining	4	299.6	11	476.2	2	80.5	5	182.6	5	217.2
	Enhanced passive	0	0.0	1	71.9	0	0.0	2	93.6	3	138.0
Rash	EHR data mining	2	149.8	2	86.6	3	120.7	4	146.1	5	217.2
	Enhanced passive	0	0.0	0	0.0	1	57.1	4	187.2	0	0.0
Respiratory/ Miscellaneous	EHR data mining	20	1,498.1	19	822.5	19	764.3	17	620.9	21	912.3
	Enhanced passive	2	182.8	6	431.3	8	457.1	16	748.7	8	368.0
Sensitivity/ Anaphylaxis	EHR data mining	1	74.9	0	0.0	1	40.2	0	0.0	0	0.0
	Enhanced passive	0	0.0	0	0.0	1	57.1	0	0.0	0	0.0

Registered Patients	EHR data mining	51,023	50,932	50,794	50,665	50,548
	Enhanced passive	28,551	28,486	28,419	28,372	28,315
Vaccinated Patients	EHR data mining	6,262	5,734	4,911	3,414	2,422
	Enhanced passive	5,583	5,120	4,486	3,725	2,734
Registered Patients	**Total**	80,831	80,796	80,727	80,720	80,582
Vaccinated Patients	**Total**	11,845	10,854	9,397	7,139	5,156

Further information:

Post-authorisation safety surveillance pilot study

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We are assessing adverse event of interest (AEI) frequencies among subjects who have received the influenza vaccine, using routinely collected data in nine primary care practices. AEIs up to 14 days from the date of vaccination are included for vaccinated patients. We are also providing the rate of these events in non-vaccinated patients, to assess background rates and trends. Where these conditions are found in non-vaccinated subjects we call them illness-disease episodes (IDE).

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This report shows the weekly data flow capturing vaccine coverage, and proportions of patients reporting possible AEIs within the EMA's surveillance condition categories. The results of this pilot will be used to assess whether the data collected in the study meet the requirements of enhanced safety surveillance as stipulated in the interim guidance issued by EMA in April 2014.

This pilot study has received [redacted] approval (REF: 15/LO/1254).

How rates of possible adverse events are calculated

Denominator: The vaccinated denominator are all registered patients in the participating practices who have received the seasonal influenza vaccine in the preceding 2 weeks. The non-vaccinated denominator are all registered patients who have not received the seasonal influenza vaccine to date.

Numerator: The numerator for the vaccinated patients is the number of possible adverse events occurring during the current study week, which happened within a 14-day window after the patient received the seasonal influenza vaccine. The numerator for the non-vaccinated patients is the number of possible adverse events occurring during the study week, for non-vaccinated patients.

Detailed numerators and denominators for the vaccinated patients are stated in graph (L), page 8.

Vaccinated and non-vaccinated comparisons

This pilot study is not designed to provide a formal comparison of the two groups, but the rates of possible AEIs in the non-vaccinated population are included to provide a crude background rate. In future years, once more data has been collected, a more accurate background rate could be established using a 5 year average.

Timeliness of the data

In routine primary care data, the date of recording may differ from the date of the event. Sometimes GPs may add an entry to the patient's record several weeks after the date of the event. Usually, this lag in recording would not be greater than 6 weeks. Therefore, it is expected that each week there may be a small variation in the AEI rates from previous weeks, as new data is recorded.

Further information:

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For further information, please contact:

Professor [redacted]
[redacted]

[redacted]

[redacted]

Post-authorisation safety study of influenza vaccine

Key Statistics:

Week Number/Year…….45/2015
Week Starting - Ending……..…02/11/2015 - 08/11/2015
No. of Practices……9
Population…….80911 (13628 vaccinated)

Post-authorisation safety study:

The European Medicines Agency (EMA) has set out new requirements for influenza vaccine safety surveillance that all Marketing Authorisation Holders (MAHs) providing vaccines in the EU must address. This pilot, funded by Glaxo-SmithKline and conducted by the [redacted] explores the use of routinely collected data in the UK to provide timely and relevant information on influenza vaccine safety.

UK primary care is highly computerised, though the major suppliers have different data models, coding systems, and methods of data access. This pilot study demonstrates the feasibility of drawing together the heterogeneous data from different brands of computer system into a single report format.

Key messages:

Vaccine exposure:

Vaccine exposure rates for all ages have **increased** from **14.89 in week 44** to **17.08 in week 45**.

Practice types:
Enhanced passive practices gave vaccinated patients a card to prompt reporting; Electronic Health Record (EHR) data mining practices have findings reported from routine data.

Possible adverse events in the vaccinated population by Enhanced passive and EHR data mining practices (per 100,000 patients):

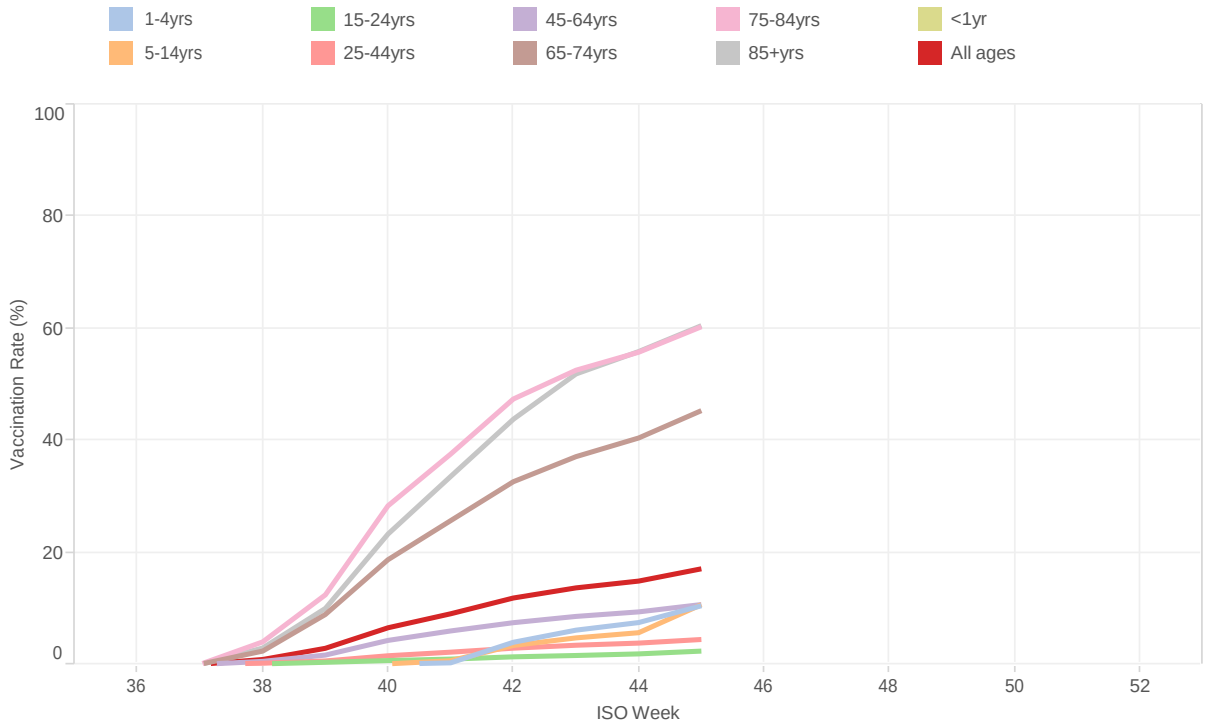
- **Fever/Pyrexia :** Enhanced passive rate was **182.8** in week 44 compared with **242.1** in week 45. EHR data mining rate was **1273.4** in week 44 compared with **264.0** in week 45.
- **Gastrointestinal :** Enhanced passive was **0.0** in week 44 compared with **80.7** in week 45. EHR data mining rate was **374.5** in week 44 compared with **198.0** in week 45.
- **General symptoms :** Enhanced passive rate was **91.4** in week 44 compared with **0.0** in week 45. EHR data mining rate was **299.6** in week 44 compared with **132.0** in week 45.
- **Local symptoms :** Enhanced passive rate was **91.4** in week 44 compared with **80.7** in week 45. EHR data mining rate was **0.0** in week 44 compared with **0.0** in week 45.
- **Musculoskeletal :** Enhanced passive rate was **274.2** in week 44 compared with **242.1** in week 45. EHR data mining rate was **524.3** in week 44 compared with **396.0** in week 45.
- **Neurological :** Enhanced passive rate was **0.0** in week 44 compared with **0.0** in week 45. EHR data mining rate was **299.6** in week 44 compared with **66.0** in week 45.
- **Rash :** Enhanced passive rate was **0.0** in week 44 compared with **161.4** in week 45. EHR data mining rate was **149.8** in week 44 compared with **66.0** in week 45.
- **Respiratory/Miscellaneous :** Enhanced passive rate was **182.8** in week 44 compared with **565.0** in week 45. EHR data mining rate was 1498.1 in week 44 compared with **528.1** in week 45.
- **Sensitivity/anaphylaxis :** Enhanced passive rate was **0.0** in week 44 compared with **0.0** in week 45. EHR data mining rate was **74.9** in week 44 compared with **0.0** in week 45.

Comment:

The proportion of the practice population vaccinated continued to increase this week. The most common possible adverse event categories this week were respiratory/miscellaneous, musculoskeletal, and fever/pyrexia.

Influenza vaccine exposure rates

(O) Cumulative vaccine exposure rates: All age groups, 2015 *



* The vaccination exposure rates are a percentage of all registered patients in the pilot practices.

(P) Cumulative vaccine exposure rates: All age groups, by vaccine brand, 2015 *

	GSK vaccine	Non-GSK vaccine
<1yr		
1-4yrs	5.87	11.40
5-14yrs	2.49	12.44
15-24yrs	2.27	2.41
25-44yrs	4.36	4.48
45-64yrs	11.48	10.51
65-74yrs	52.09	43.50
75-84yrs	72.55	56.64
85+yrs	69.59	57.87
All ages	20.47	16.28

* The GSK vaccine rates are based on the vaccine exposure rates in 2 out of 9 of the pilot practices.

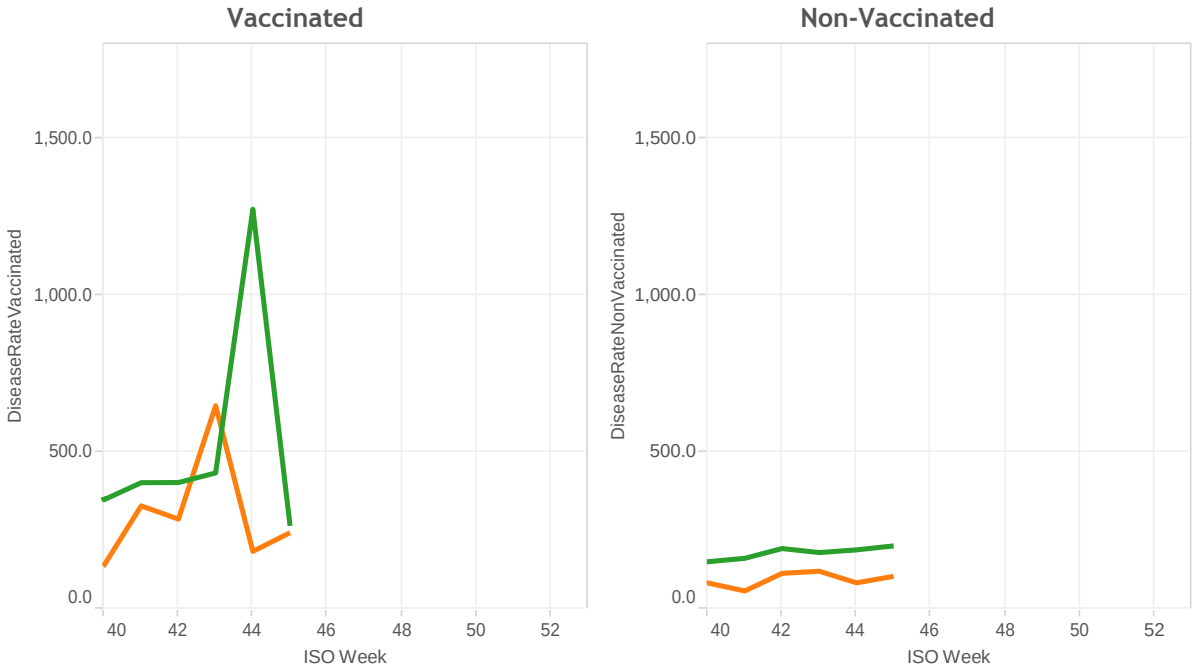
(Q) Key denominators

	Registered Patients	Vaccinated Patients	Vaccination Rate
Non-GSK vaccine	64,584	10,517	16.28
GSK vaccine	15,200	3,111	20.47
Grand Total	80,911	13,628	17.08

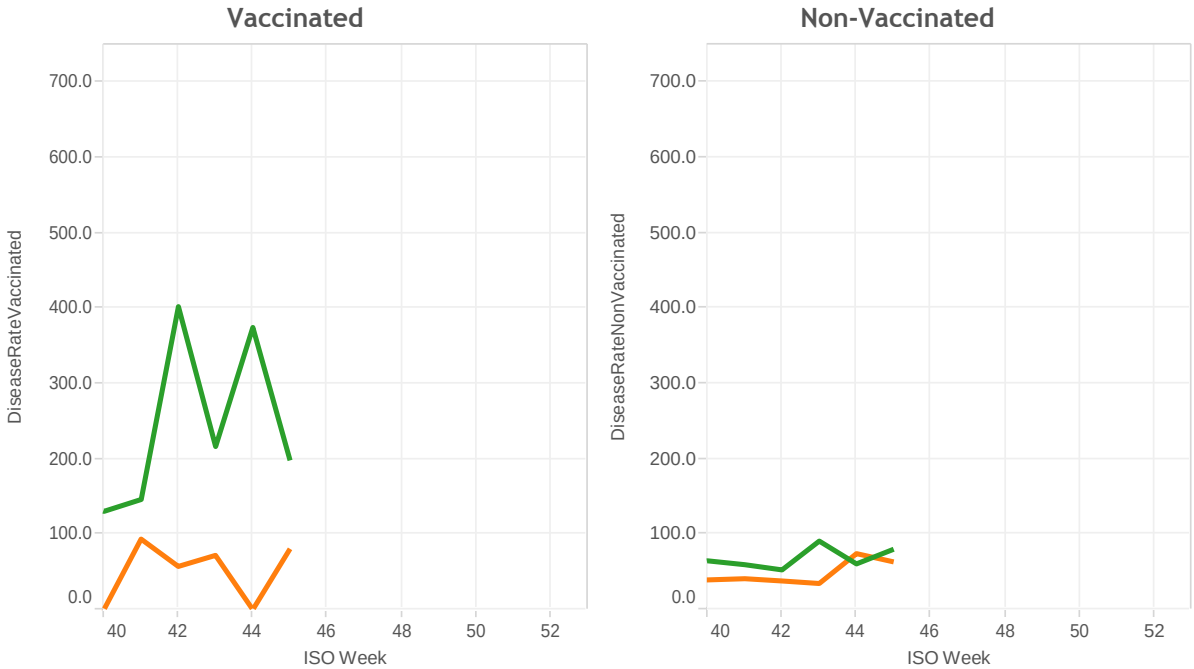
	Registered Patients	Vaccinated Patients	Vaccination Rate
EHR data mining	51,151	7,262	14.20
Enhanced passive	28,633	6,366	22.23
Grand Total	80,911	13,628	17.08

Possible adverse event rates by EMA surveillance condition

(R) Fever/Pyrexia by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015

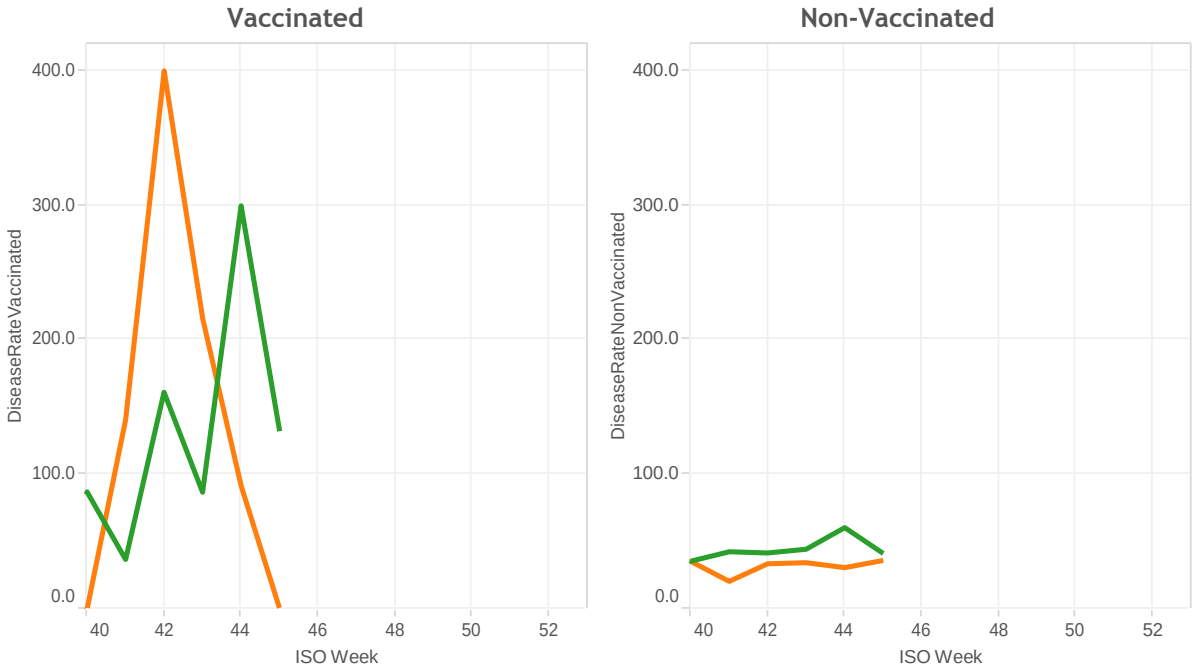


(S) Gastrointestinal by Enhanced passive or EHR data mining practices practices: Incidence rates per 100,000, 2015

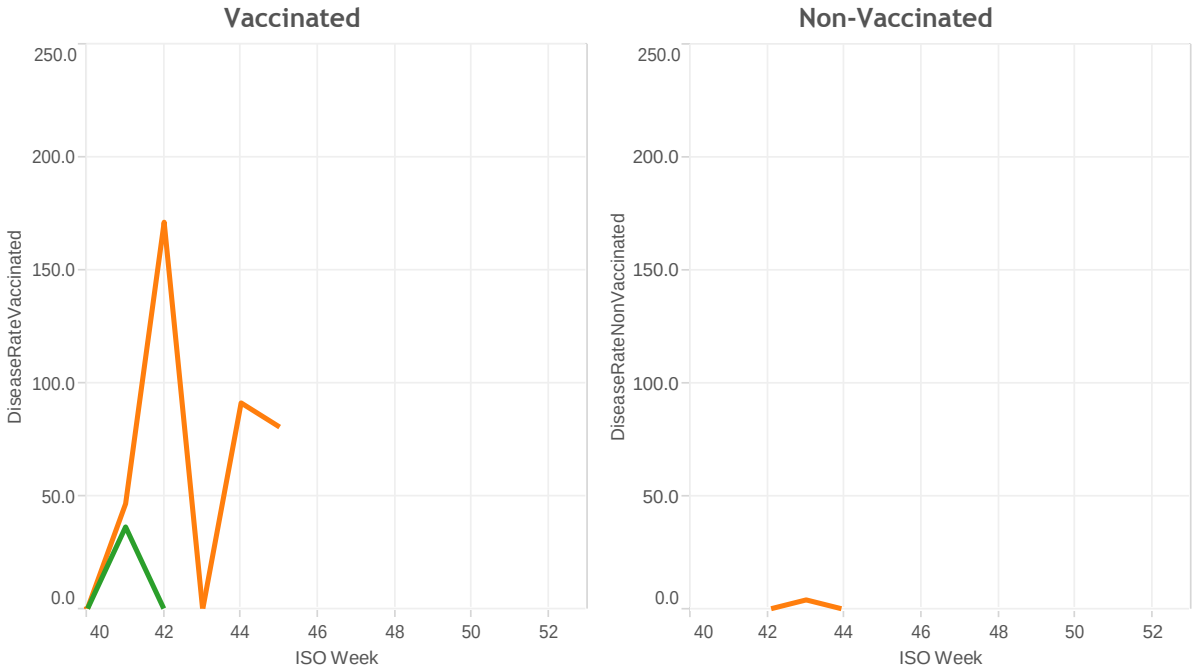


Possible adverse event rates by EMA surveillance condition

(T) General non-specific symptoms by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015

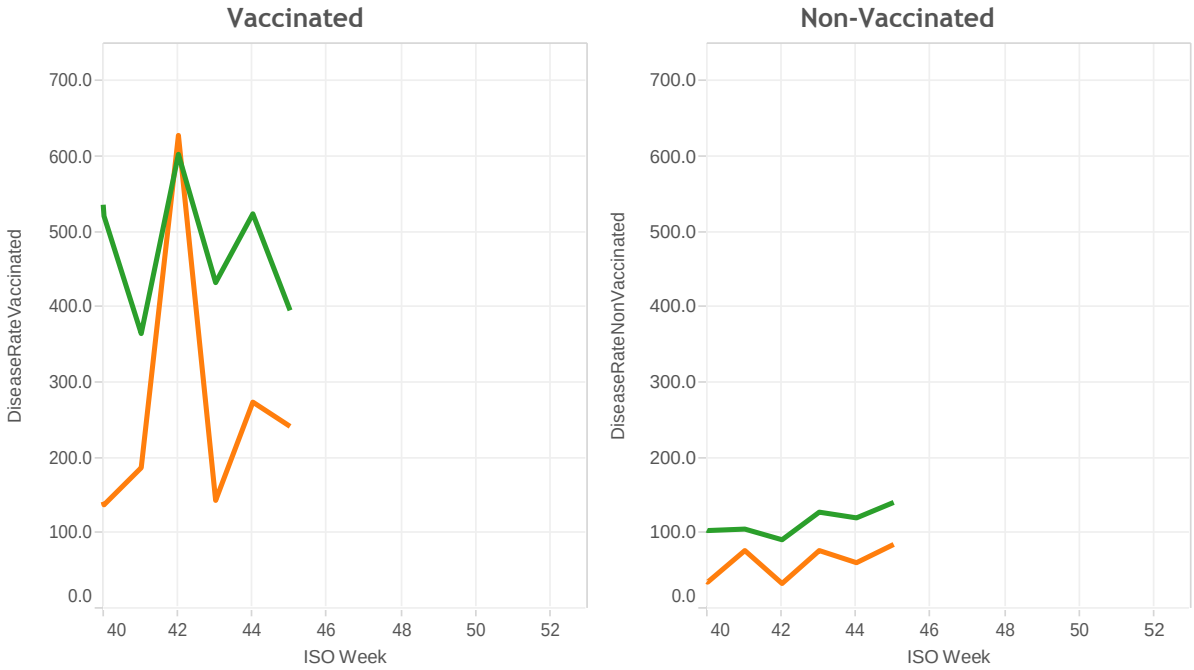


(U) Local symptoms by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015

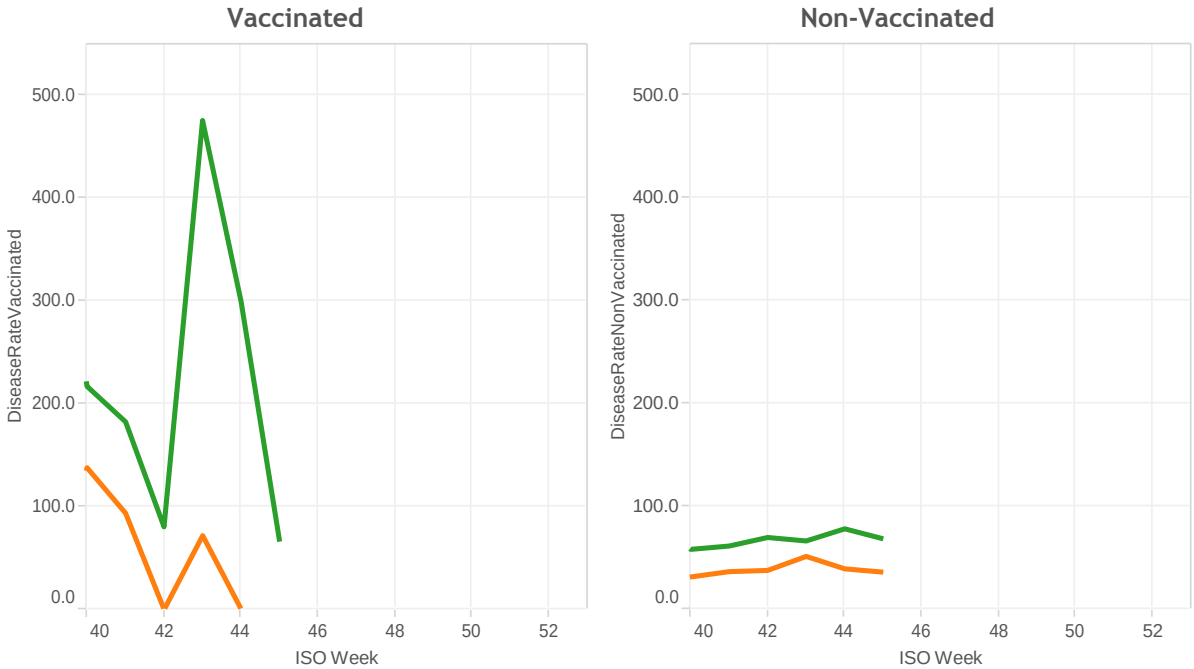


Possible adverse event rates by EMA surveillance condition

(V) Musculoskeletal by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015

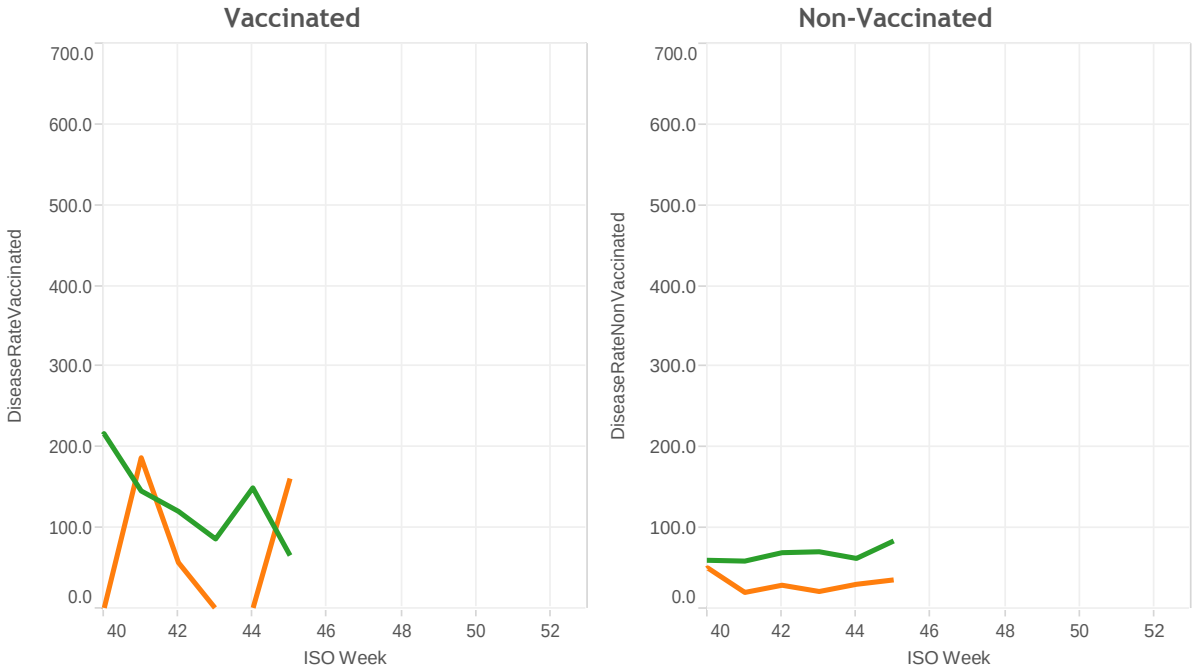


(W) Neurological by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015

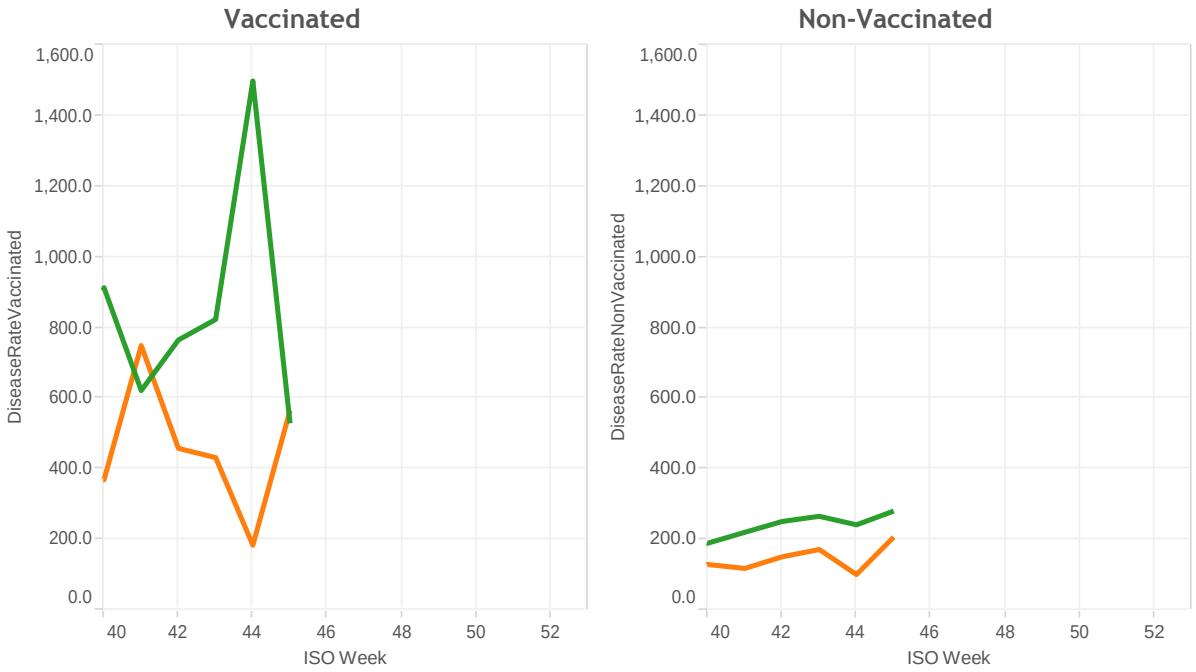


Possible adverse event rates by EMA surveillance condition

(X) Rash by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015

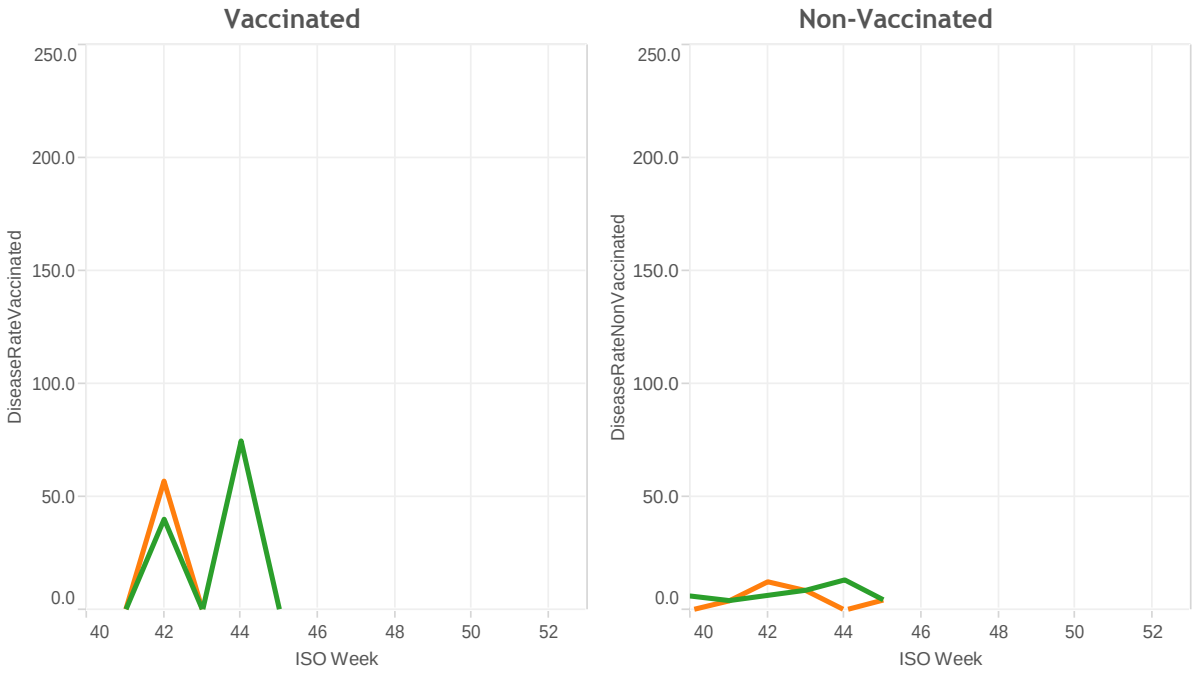


(Y) Respiratory/Miscellaneous by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015



Possible adverse event rates by EMA surveillance condition, and weekly summary by vaccine brand

(Z) Sensitivity/Anaphylaxis by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015



(AA) Possible adverse events by GSK or non-GSK vaccines: Incidence rates per 100,000, 2015 **

		Week number 45	44	43	42	41
		Week beginning 02/11/2015	26/10/2015	19/10/2015	12/10/2015	05/10/2015
		Week ending 08/11/2015	01/11/2015	25/10/2015	18/10/2015	11/10/2015
Fever/Pyrexia	GSK	511.1	148.8	669.3	513.5	742.3
	Non-GSK	184.6	1,024.5	473.9	318.2	279.8
Gastrointestinal	GSK	170.4	0.0	0.0	0.0	212.1
	Non-GSK	138.4	284.6	203.1	318.2	101.7
General symptoms	GSK	0.0	0.0	267.7	385.1	212.1
	Non-GSK	92.3	284.6	101.6	231.4	50.9
Local symptoms	GSK	170.4	148.8	0.0	256.7	106.0
	Non-GSK	0.0	0.0	0.0	28.9	25.4
Musculoskeletal	GSK	511.1	446.4	267.7	1,412.1	424.2
	Non-GSK	276.9	398.4	338.5	433.9	254.3
Neurological	GSK	0.0	0.0	133.9	0.0	106.0
	Non-GSK	46.1	227.7	372.4	57.9	152.6
Rash	GSK	340.7	0.0	0.0	128.4	424.2
	Non-GSK	46.1	113.8	67.7	86.8	101.7
Respiratory/Miscellaneous	GSK	511.1	148.8	535.5	641.8	1,166.5
	Non-GSK	553.8	1,195.2	710.9	636.4	559.5
Sensitivity/Anaphylaxis	GSK	0.0	0.0	0.0	128.4	0.0
	Non-GSK	0.0	56.9	0.0	28.9	0.0
		0.0 200.0 400.0	0.0 200.0 400.0	0.0 200.0 400.0	0.0 200.0 400.0	0.0 200.0 400.0

** It must be noted that the two GSK practices are both conducting enhanced passive surveillance.

Weekly summary of possible adverse event rates by EMA surveillance condition and practice type

(BB) Possible adverse events by Enhanced passive or EHR data mining practices: Incidence rates per 100,000 and count of episodes, 2015

Week number		45		44		43		42		41	
Week beginning		02/11/2015		26/10/2015		19/10/2015		12/10/2015		05/10/2015	
Week ending		08/11/2015		01/11/2015		25/10/2015		18/10/2015		11/10/2015	
		Episodes	Rate	Episodes	Rate	Episodes	Rate	Episodes	Rate	Episodes	Rate
Fever/Pyrexia	EHR data mining	4	264.0	17	1,273.4	10	432.9	10	402.3	11	401.8
	Enhanced passive	3	242.1	2	182.8	9	647.0	5	285.7	7	327.6
Gastrointestinal	EHR data mining	3	198.0	5	374.5	5	216.5	10	402.3	4	146.1
	Enhanced passive	1	80.7	0	0.0	1	71.9	1	57.1	2	93.6
General symptoms	EHR data mining	2	132.0	4	299.6	2	86.6	4	160.9	1	36.5
	Enhanced passive	0	0.0	1	91.4	3	215.7	7	400.0	3	140.4
Local symptoms	EHR data mining	0	0.0	0	0.0	0	0.0	0	0.0	1	36.5
	Enhanced passive	1	80.7	1	91.4	0	0.0	3	171.4	1	46.8
Musculoskeletal	EHR data mining	6	396.0	7	524.3	10	432.9	15	603.4	10	365.2
	Enhanced passive	3	242.1	3	274.2	2	143.8	11	628.6	4	187.2
Neurological	EHR data mining	1	66.0	4	299.6	11	476.2	2	80.5	5	182.6
	Enhanced passive	0	0.0	0	0.0	1	71.9	0	0.0	2	93.6
Rash	EHR data mining	1	66.0	2	149.8	2	86.6	3	120.7	4	146.1
	Enhanced passive	2	161.4	0	0.0	0	0.0	1	57.1	4	187.2
Respiratory/ Miscellaneous	EHR data mining	8	528.1	20	1,498.1	19	822.5	19	764.3	17	620.9
	Enhanced passive	7	565.0	2	182.8	6	431.3	8	457.1	16	748.7
Sensitivity/ Anaphylaxis	EHR data mining	0	0.0	1	74.9	0	0.0	1	40.2	0	0.0
	Enhanced passive	0	0.0	0	0.0	0	0.0	1	57.1	0	0.0

Registered Patients	EHR data mining	51,151	51,023	50,932	50,794	50,665
	Enhanced passive	28,633	28,551	28,486	28,419	28,372
Vaccinated Patients	EHR data mining	7,262	6,262	5,734	4,911	3,414
	Enhanced passive	6,366	5,583	5,120	4,486	3,725
Registered Patients	**Total**	80,911	80,831	80,796	80,727	80,720
Vaccinated Patients	**Total**	13,628	11,845	10,854	9,397	7,139

Further information:

Post-authorisation safety surveillance pilot study

The European Medicines Agency (EMA) has set out new requirements for influenza vaccine safety surveillance that all Marketing Authorisation Holders (MAHs) providing vaccines in the EU must address. This pilot, funded by GlaxoSmithKline and conducted by the [redacted] demonstrates the potential of routinely collected data in the UK to provide timely and relevant information on influenza vaccine safety.

We are assessing adverse event of interest (AEI) frequencies among subjects who have received the influenza vaccine, using routinely collected data in nine primary care practices. AEIs up to 14 days from the date of vaccination are included for vaccinated patients. We are also providing the rate of these events in non-vaccinated patients, to assess background rates and trends. Where these conditions are found in non-vaccinated subjects we call them illness-disease episodes (IDE).

Three practices are taking part in the enhanced passive surveillance sub-study, where a reporting card has been given to vaccinated patients to return to the practices.

This report shows the weekly data flow capturing vaccine coverage, and proportions of patients reporting possible AEIs within the EMA's surveillance condition categories. The results of this pilot will be used to assess whether the data collected in the study meet the requirements of enhanced safety surveillance as stipulated in the interim guidance issued by EMA in April 2014.

This pilot study has received [redacted] approval (REF: 15/LO/1254).

How rates of possible adverse events are calculated

Denominator: The vaccinated denominator are all registered patients in the participating practices who have received the seasonal influenza vaccine in the preceding 2 weeks. The non-vaccinated denominator are all registered patients who have not received the seasonal influenza vaccine to date.

Numerator: The numerator for the vaccinated patients is the number of possible adverse events occurring during the current study week, which happened within a 14-day window after the patient received the seasonal influenza vaccine. The numerator for the non-vaccinated patients is the number of possible adverse events occurring during the study week, for non-vaccinated patients.

Detailed numerators and denominators for the vaccinated patients are stated in graph (L), page 8.

Vaccinated and non-vaccinated comparisons

This pilot study is not designed to provide a formal comparison of the two groups, but the rates of possible AEIs in the non-vaccinated population are included to provide a crude background rate. In future years, once more data has been collected, a more accurate background rate could be established using a 5 year average.

Timeliness of the data

In routine primary care data, the date of recording may differ from the date of the event. Sometimes GPs may add an entry to the patient's record several weeks after the date of the event. Usually, this lag in recording would not be greater than 6 weeks. Therefore, it is expected that each week there may be a small variation in the AEI rates from previous weeks, as new data is recorded.

Further information:

Data extraction process and information governance

Data are extracted twice weekly from practice systems by Apollo Medical Systems on behalf of the [redacted] Patients who have withheld consent for data sharing are excluded from the extraction process. Data are pseudonymised as close to source as possible.

Data are held on secure servers at the Section of Clinical Medicine and Ageing at the [redacted] Both Apollo and the [redacted] are registered and compliant with the Data Protection Act and fully compliant with all relevant HSCIC and NHS data information governance best practice.

For further information, please contact:

Professor [redacted]
[redacted]

[redacted]

[redacted]

Post-authorisation safety study of influenza vaccine

Key Statistics:

Week Number/Year…….46/2015
Week Starting - Ending……..…09/11/2015 - 15/11/2015
No. of Practices……9
Population…….80936 (14404 vaccinated)

Post-authorisation safety study:

The European Medicines Agency (EMA) has set out new requirements for influenza vaccine safety surveillance that all Marketing Authorisation Holders (MAHs) providing vaccines in the EU must address. This pilot, funded by Glaxo-SmithKline and conducted by the [redacted] explores the use of routinely collected data in the UK to provide timely and relevant information on influenza vaccine safety.

UK primary care is highly computerised, though the major suppliers have different data models, coding systems, and methods of data access. This pilot study demonstrates the feasibility of drawing together the heterogeneous data from different brands of computer system into a single report format.

Key messages:

Vaccine exposure:

Vaccine exposure rates for all ages have **increased** from **17.08 in week 45** to **18.02 in week 46**.

Practice types:
Enhanced passive practices gave vaccinated patients a card to prompt reporting; Electroning Health Record (EHR) data mining practices have findings reported from routine data.

Possible adverse events in the vaccinated population by Enhanced passive and EHR data mining practices (per 100,000 patients):

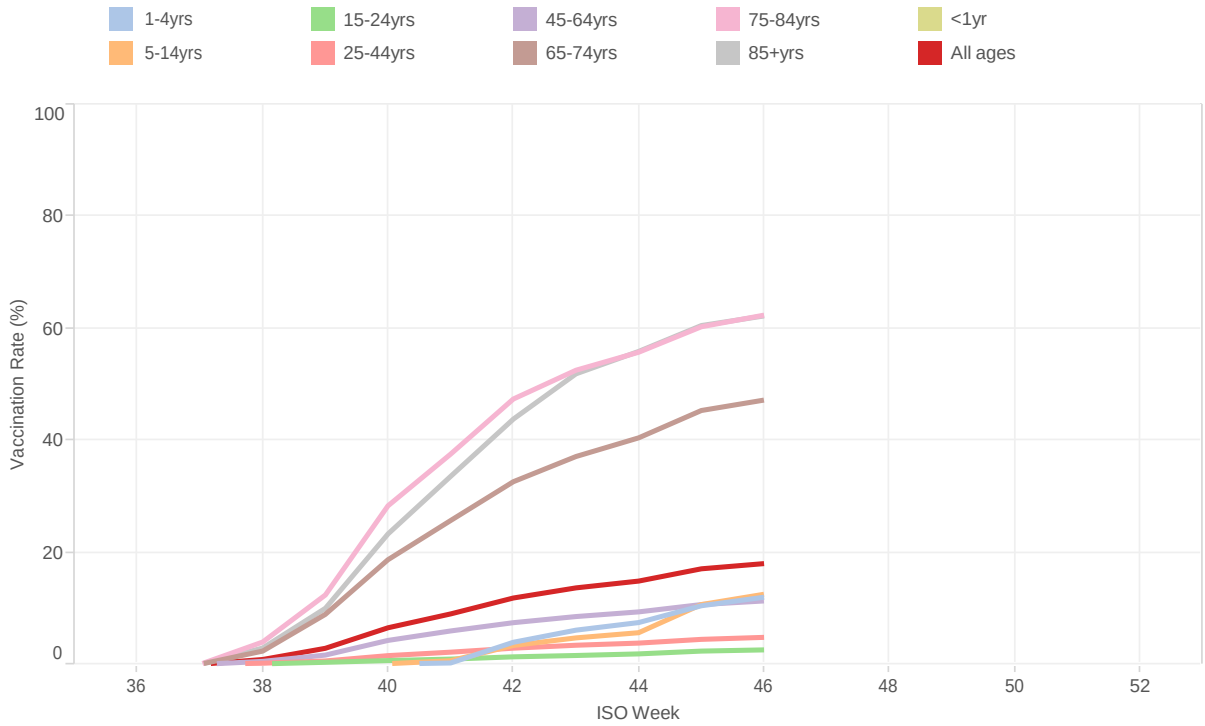
- **Fever/Pyrexia :** Enhanced passive rate was **242.1** in week 45 compared with **0.0** in week 46. EHR data mining rate was **264.0** in week 45 compared with **407.6** in week 46.
- **Gastrointestinal :** Enhanced passive rate was **80.7** in week 45 compared with **0.0** in week 46. EHR data mining rate was **198.0** in week 45 compared with **0.0** in week 46.
- **General symptoms :** Enhanced passive rate was **0.0** in week 45 compared with **0.0** in week 46. EHR data mining rate was **132.0** in week 45 compared with **339.7** in week 46.
- **Local symptoms :** Enhanced passive rate was **80.7** in week 45 compared with **0.0** in week 46. EHR data mining rate was **0.0** in week 45 compared with **0.0** in week 46.
- **Musculoskeletal :** Enhanced passive rate was **242.1** in week 45 compared with **188.7** in week 46. EHR data mining rate was **396.0** in week 45 compared with **475.5** in week 46.
- **Neurological :** Enhanced passive rate was **0.0** in week 45 compared with **94.3** in week 46. EHR data mining rate was **66.0** in week 45 compared with **203.8** in week 46.
- **Rash :** Enhanced passive rate was **161.4** in week 45 compared with **94.3** in week 46. EHR data mining rate was
- in week 45 compared with **135.9** in week 46.
- **Respiratory/Miscellaneous :** Enhanced passive rate was **565.0** in week 45 compared with **94.3** in week 46. EHR data mining rate was **528.1** in week 45 compared with **815.2** in week 46.
- **Sensitivity/anaphylaxis :** Enhanced passive rate was **0.0** in week 45 compared with **0.0** in week 46. EHR data mining rate was **0.0** in week 45 compared with **67.9** in week 46.

Comment:

The proportion of the practice population vaccinated continued to increase this week. The most common possible adverse event categories this week were respiratory/miscellaneous, and musculoskeletal.

Influenza vaccine exposure rates

- **Cumulative vaccine exposure rates: All age groups, 2015 ***



* The vaccination exposure rates are a percentage of all registered patients in the pilot practices.

- **Cumulative vaccine exposure rates: All age groups, by vaccine brand, 2015 ***

	GSK vaccine	Non-GSK vaccine
<1yr		
1-4yrs	6.87	13.04
5-14yrs	3.12	14.56
15-24yrs	2.74	2.58
25-44yrs	4.91	4.82
45-64yrs	12.46	11.07
65-74yrs	55.65	44.92
75-84yrs	76.65	58.11
85+yrs	72.97	59.10
All ages	21.92	17.10

* The GSK vaccine rates are based on the vaccine exposure rates in 2 out of 9 of the pilot practices.

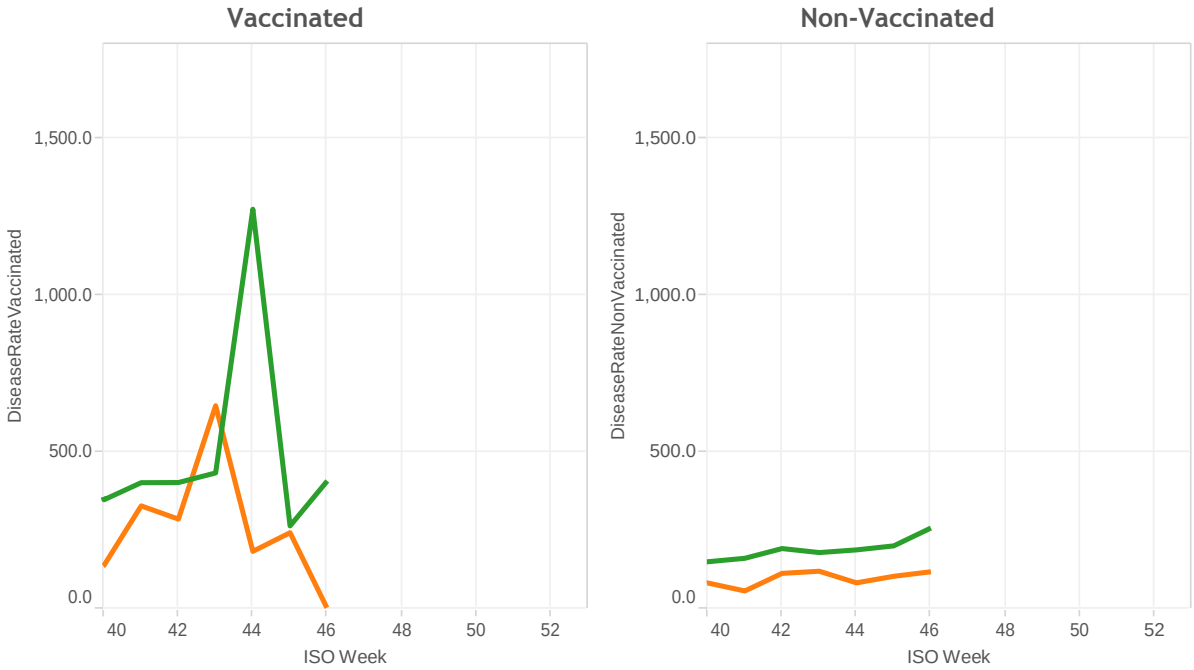
- **Key denominators**

	Registered Patients	Vaccinated Patients	Vaccination Rate
Non-GSK vaccine	64,696	11,063	17.10
GSK vaccine	15,243	3,341	21.92
Grand Total	80,936	14,404	18.02

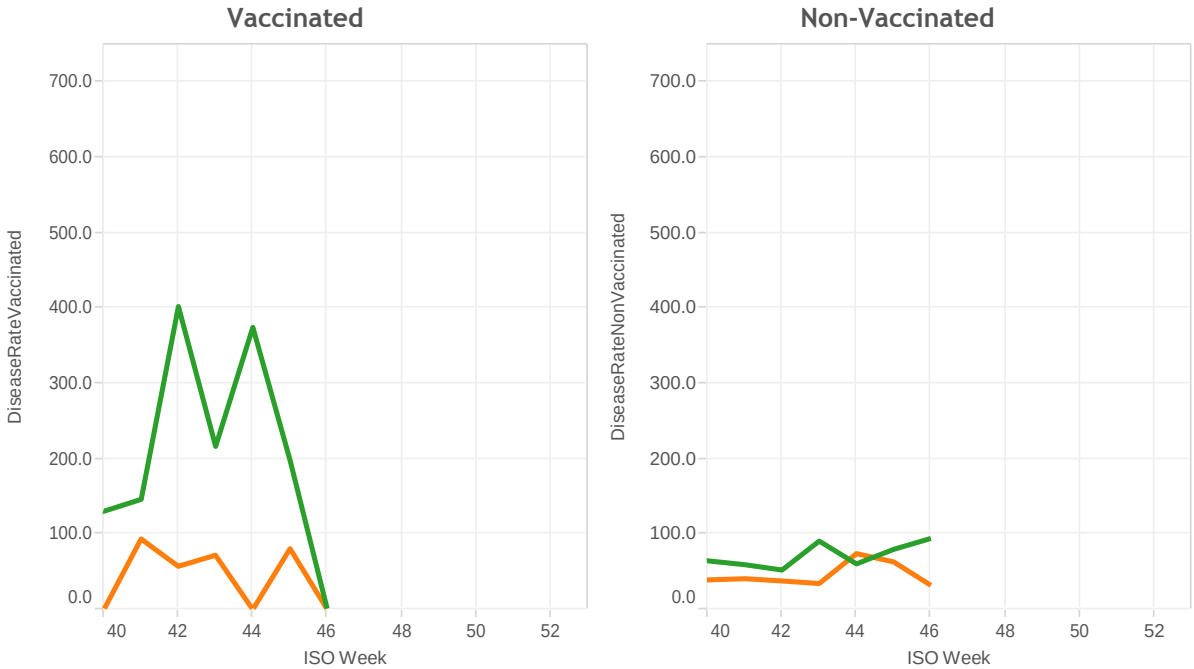
	Registered Patients	Vaccinated Patients	Vaccination Rate
EHR data mining	51,236	7,748	15.12
Enhanced passive	28,703	6,656	23.19
Grand Total	80,936	14,404	18.02

Possible adverse event rates by EMA surveillance condition

- **Fever/Pyrexia by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

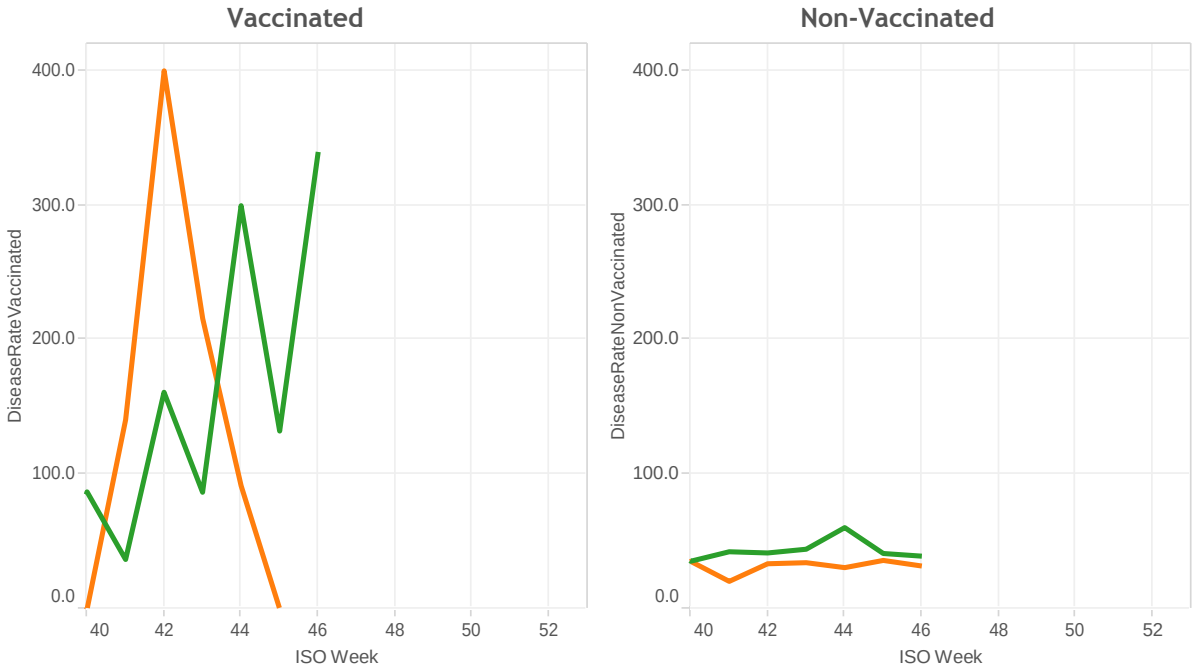


- **Gastrointestinal by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

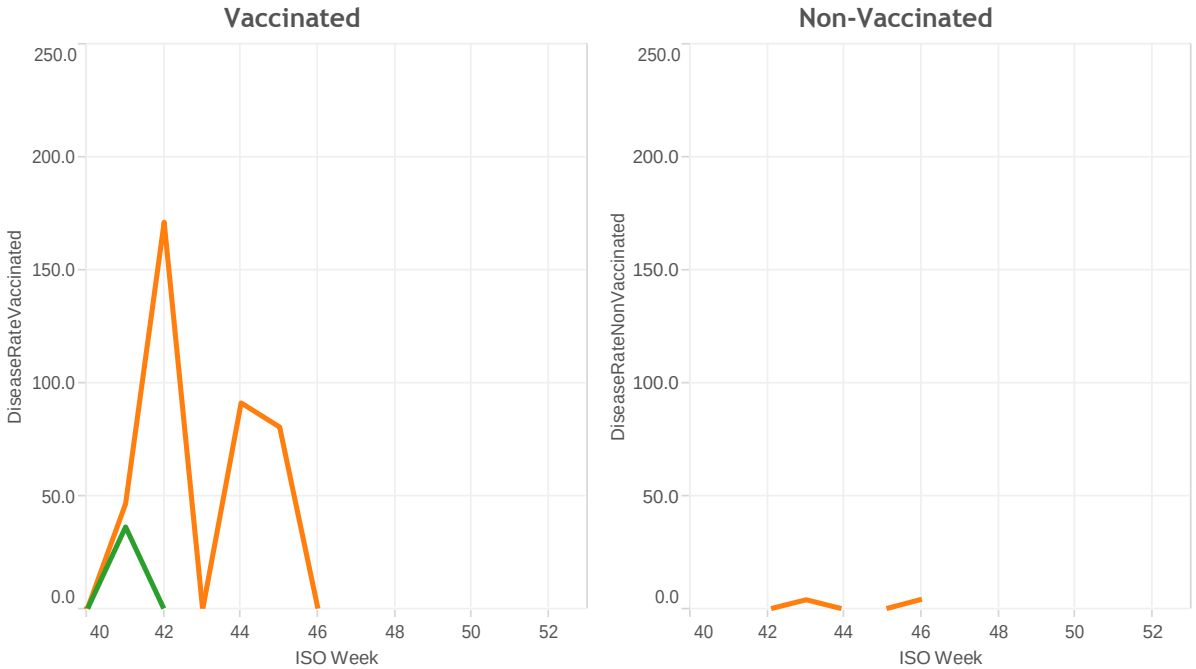


Possible adverse event rates by EMA surveillance condition

- **General non-specific symptoms by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

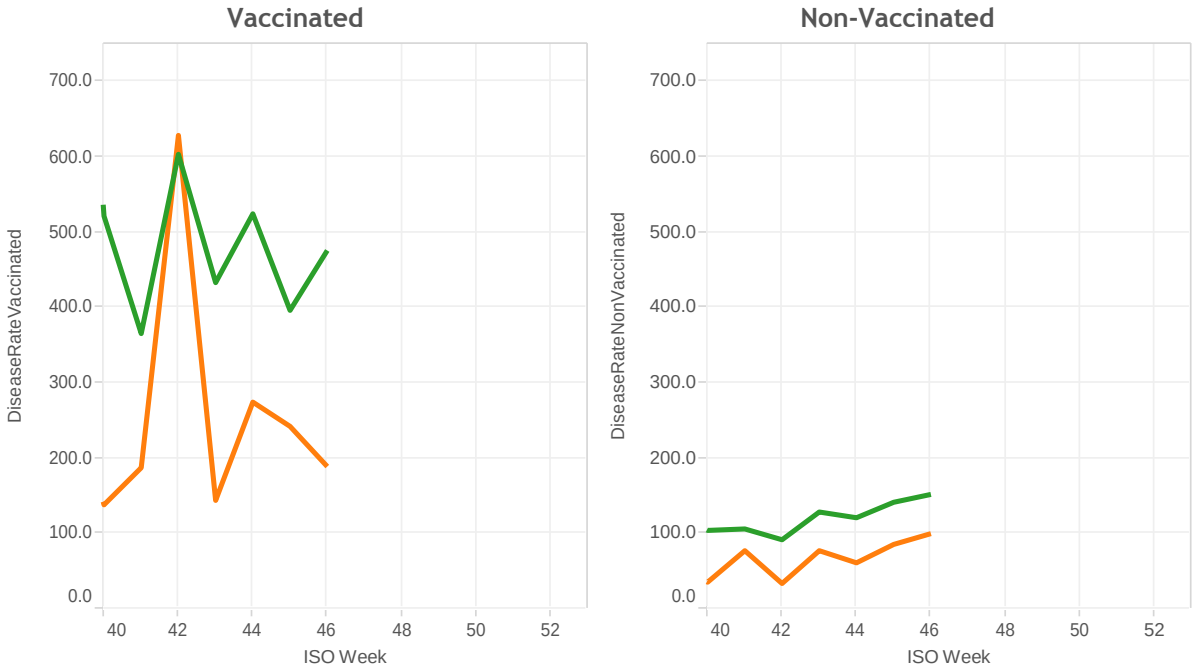


- **Local symptoms by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

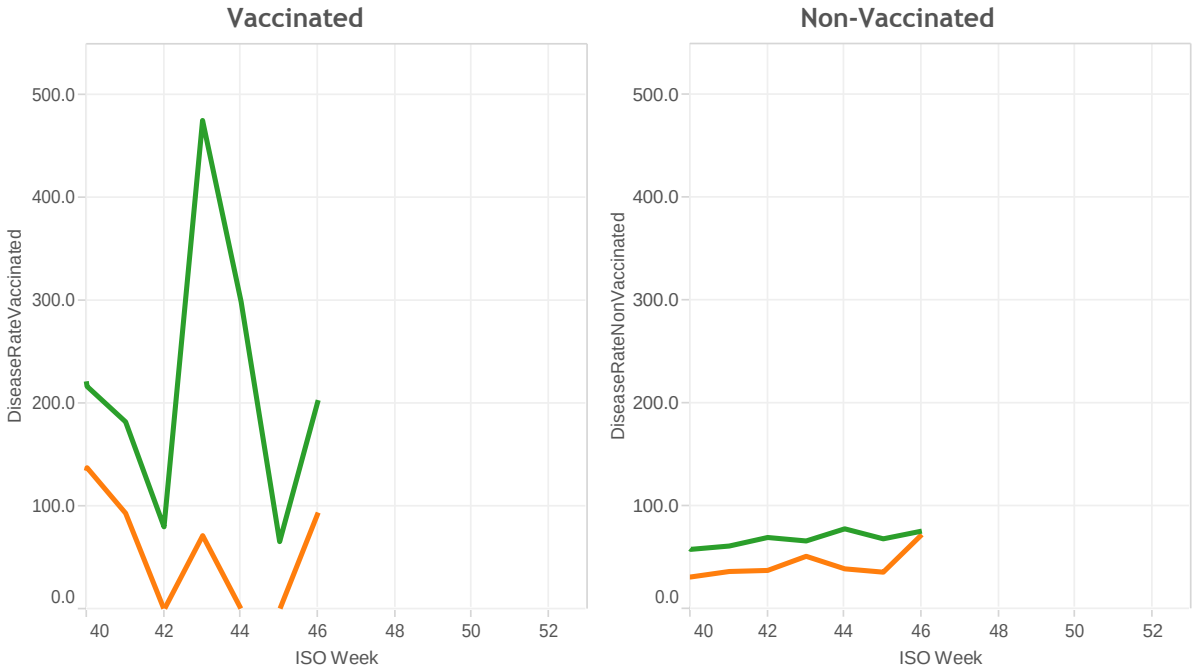


Possible adverse event rates by EMA surveillance condition

- **Musculoskeletal by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

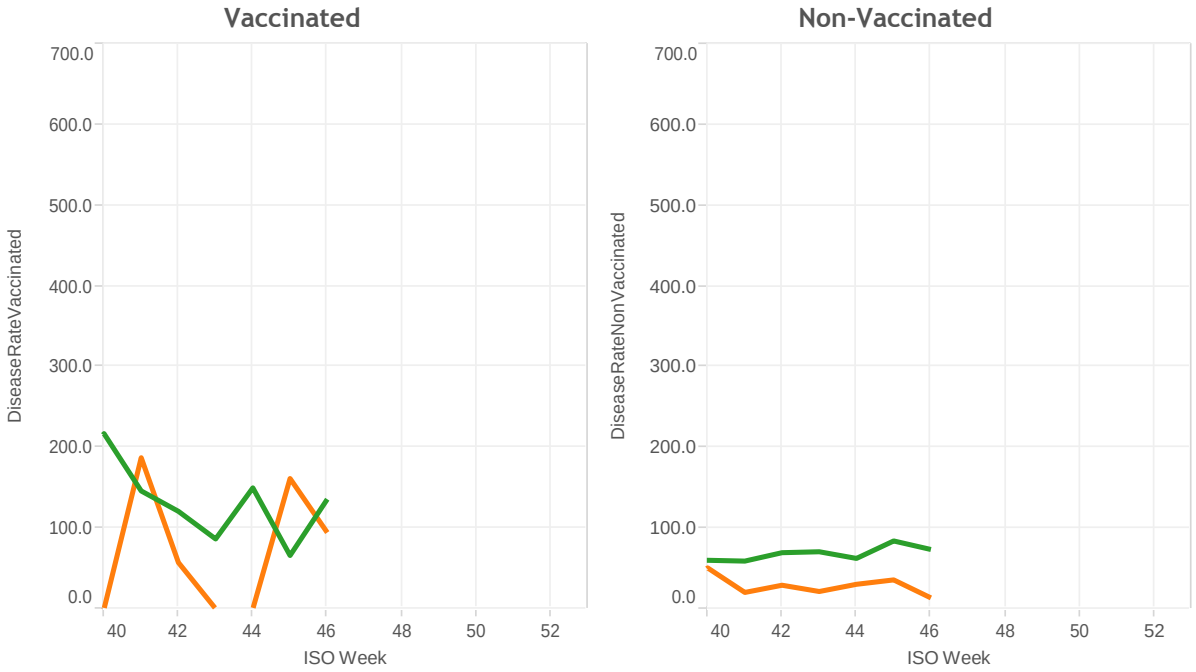


- **Neurological by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

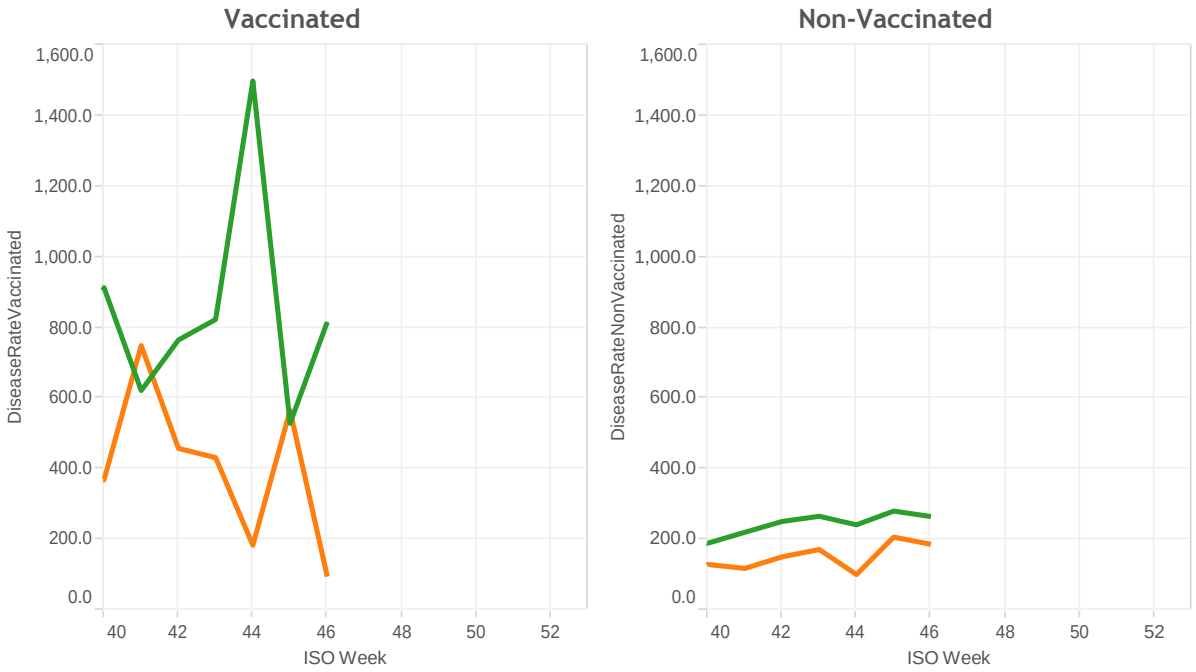


Possible adverse event rates by EMA surveillance condition

- **Rash by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**



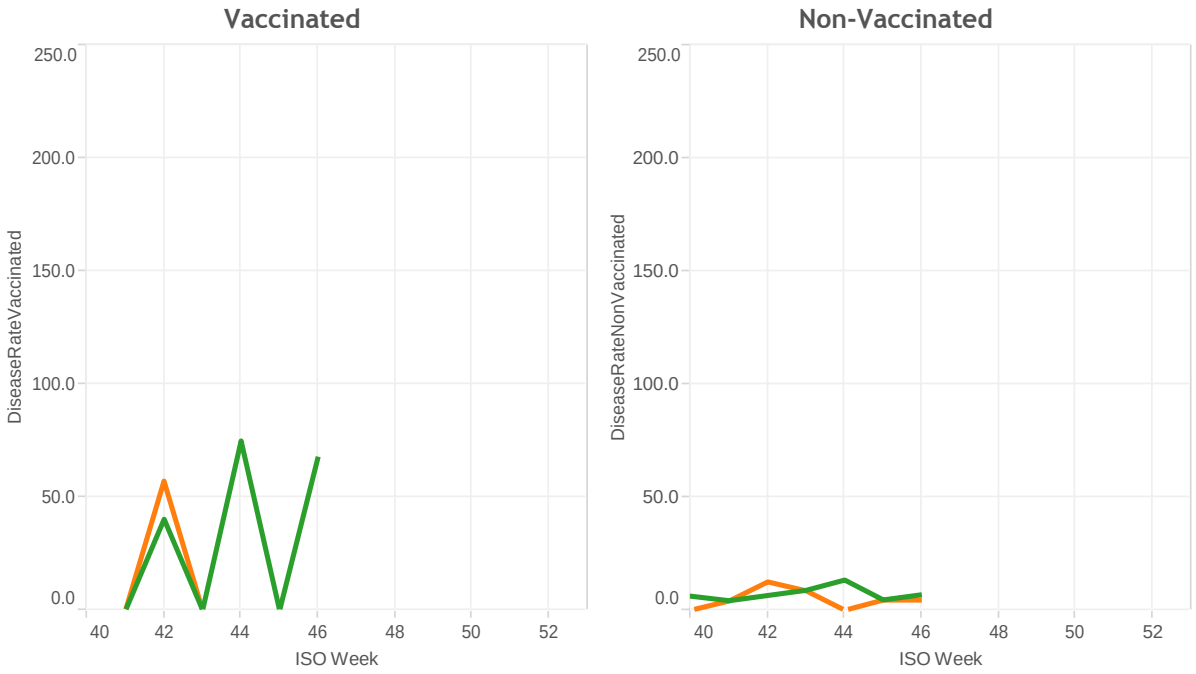
- **Respiratory/Miscellaneous by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**



Possible adverse event rates by EMA surveillance condition, and weekly summary by vaccine brand

EHR data mining Enhanced passive

- **Sensitivity/Anaphylaxis by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**



- **Possible adverse events by GSK or non-GSK vaccines: Incidence rates per 100,000, 2015 ****

Week number		46	45	44	43	42
Week beginning		09/11/2015	02/11/2015	26/10/2015	19/10/2015	12/10/2015
Week ending		15/11/2015	08/11/2015	01/11/2015	25/10/2015	18/10/2015
Fever/Pyrexia	GSK	0.0	511.1	148.8	669.3	513.5
	Non-GSK	303.3	184.6	1,024.5	473.9	318.2
Gastrointestinal	GSK	0.0	170.4	0.0	0.0	0.0
	Non-GSK	0.0	138.4	284.6	203.1	318.2
General symptoms	GSK	0.0	0.0	0.0	267.7	385.1
	Non-GSK	252.8	92.3	284.6	101.6	231.4
Local symptoms	GSK	0.0	170.4	148.8	0.0	256.7
	Non-GSK	0.0	0.0	0.0	0.0	28.9
Musculoskeletal	GSK	361.0	511.1	446.4	267.7	1,412.1
	Non-GSK	353.9	276.9	398.4	338.5	433.9
Neurological	GSK	180.5	0.0	0.0	133.9	0.0
	Non-GSK	151.7	46.1	227.7	372.4	57.9
Rash	GSK	180.5	340.7	0.0	0.0	128.4
	Non-GSK	101.1	46.1	113.8	67.7	86.8
Respiratory/Miscellaneous	GSK	180.5	511.1	148.8	535.5	641.8
	Non-GSK	606.7	553.8	1,195.2	710.9	636.4
Sensitivity/Anaphylaxis	GSK	0.0	0.0	0.0	0.0	128.4
	Non-GSK	50.6	0.0	56.9	0.0	28.9

0.0 200.0 400.0

** It must be noted that the two GSK practices are both conducting enhanced passive surveillance.

Weekly summary of possible adverse event rates by EMA surveillance condition and practice type

- **Possible adverse events by Enhanced passive or EHR data mining practices: Incidence rates per 100,000 and count of episodes, 2015**

Week number		46		45		44		43		42	
Week beginning		09/11/2015		02/11/2015		26/10/2015		19/10/2015		12/10/2015	
Week ending		15/11/2015		08/11/2015		01/11/2015		25/10/2015		18/10/2015	
		Episodes	Rate	Episodes	Rate	Episodes	Rate	Episodes	Rate	Episodes	Rate
Fever/Pyrexia	EHR data mining	6	407.6	4	264.0	17	1,273.4	10	432.9	10	402.3
	Enhanced passive	0	0.0	3	242.1	2	182.8	9	647.0	5	285.7
Gastrointestinal	EHR data mining	0	0.0	3	198.0	5	374.5	5	216.5	10	402.3
	Enhanced passive	0	0.0	1	80.7	0	0.0	1	71.9	1	57.1
General symptoms	EHR data mining	5	339.7	2	132.0	4	299.6	2	86.6	4	160.9
	Enhanced passive	0	0.0	0	0.0	1	91.4	3	215.7	7	400.0
Local symptoms	EHR data mining	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Enhanced passive	0	0.0	1	80.7	1	91.4	0	0.0	3	171.4
Musculoskeletal	EHR data mining	7	475.5	6	396.0	7	524.3	10	432.9	15	603.4
	Enhanced passive	2	188.7	3	242.1	3	274.2	2	143.8	11	628.6
Neurological	EHR data mining	3	203.8	1	66.0	4	299.6	11	476.2	2	80.5
	Enhanced passive	1	94.3	0	0.0	0	0.0	1	71.9	0	0.0
Rash	EHR data mining	2	135.9	1	66.0	2	149.8	2	86.6	3	120.7
	Enhanced passive	1	94.3	2	161.4	0	0.0	0	0.0	1	57.1
Respiratory/ Miscellaneous	EHR data mining	12	815.2	8	528.1	20	1,498.1	19	822.5	19	764.3
	Enhanced passive	1	94.3	7	565.0	2	182.8	6	431.3	8	457.1
Sensitivity/ Anaphylaxis	EHR data mining	1	67.9	0	0.0	1	74.9	0	0.0	1	40.2
	Enhanced passive	0	0.0	0	0.0	0	0.0	0	0.0	1	57.1

Registered Patients	EHR data mining	51,236	51,151	51,023	50,932	50,794
	Enhanced passive	28,703	28,633	28,551	28,486	28,419
Vaccinated Patients	EHR data mining	7,748	7,262	6,262	5,734	4,911
	Enhanced passive	6,656	6,366	5,583	5,120	4,486
Registered Patients	**Total**	80,936	80,911	80,831	80,796	80,727
Vaccinated Patients	**Total**	14,404	13,628	11,845	10,854	9,397

Further information:

Post-authorisation safety surveillance pilot study

The European Medicines Agency (EMA) has set out new requirements for influenza vaccine safety surveillance that all Marketing Authorisation Holders (MAHs) providing vaccines in the EU must address. This pilot, funded by GlaxoSmithKline and conducted by the [redacted] demonstrates the potential of routinely collected data in the UK to provide timely and relevant information on influenza vaccine safety.

We are assessing adverse event of interest (AEI) frequencies among subjects who have received the influenza vaccine, using routinely collected data in nine primary care practices. AEIs up to 14 days from the date of vaccination are included for vaccinated patients. We are also providing the rate of these events in non-vaccinated patients, to assess background rates and trends. Where these conditions are found in non-vaccinated subjects we call them illness-disease episodes (IDE).

Three practices are taking part in the enhanced passive surveillance sub-study, where a reporting card has been given to vaccinated patients to return to the practices.

This report shows the weekly data flow capturing vaccine coverage, and proportions of patients reporting possible AEIs within the EMA's surveillance condition categories. The results of this pilot will be used to assess whether the data collected in the study meet the requirements of enhanced safety surveillance as stipulated in the interim guidance issued by EMA in April 2014.

This pilot study has received [redacted] approval (REF: 15/LO/1254).

How rates of possible adverse events are calculated

Denominator: The vaccinated denominator are all registered patients in the participating practices who have received the seasonal influenza vaccine in the preceding 2 weeks. The non-vaccinated denominator are all registered patients who have not received the seasonal influenza vaccine to date.

Numerator: The numerator for the vaccinated patients is the number of possible adverse events occurring during the current study week, which happened within a 14-day window after the patient received the seasonal influenza vaccine. The numerator for the non-vaccinated patients is the number of possible adverse events occurring during the study week, for non-vaccinated patients.

Detailed numerators and denominators for the vaccinated patients are stated in graph (L), page 8.

Vaccinated and non-vaccinated comparisons

This pilot study is not designed to provide a formal comparison of the two groups, but the rates of possible AEIs in the non-vaccinated population are included to provide a crude background rate. In future years, once more data has been collected, a more accurate background rate could be established using a 5 year average.

Timeliness of the data

In routine primary care data, the date of recording may differ from the date of the event. Sometimes GPs may add an entry to the patient's record several weeks after the date of the event. Usually, this lag in recording would not be greater than 6 weeks. Therefore, it is expected that each week there may be a small variation in the AEI rates from previous weeks, as new data is recorded.

Further information:

Data extraction process and information governance

Data are extracted twice weekly from practice systems by Apollo Medical Systems on behalf of the [redacted] Patients who have withheld consent for data sharing are excluded from the extraction process. Data are pseudonymised as close to source as possible.

Data are held on secure servers at the Section of Clinical Medicine and Ageing at the [redacted] Both Apollo and the [redacted] are registered and compliant with the Data Protection Act and fully compliant with all relevant HSCIC and NHS data information governance best practice.

For further information, please contact:

Professor [redacted]
[redacted]

[redacted]

[redacted]

Post-authorisation safety study of influenza vaccine

Key Statistics:

Week Number/Year…….47/2015
Week Starting - Ending……..…16/11/2015 - 22/11/2015
No. of Practices……9
Population…….80955 (14934 vaccinated)

Post-authorisation safety study:

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UK primary care is highly computerised, though the major suppliers have different data models, coding systems, and methods of data access. This pilot study demonstrates the feasibility of drawing together the heterogeneous data from different brands of computer system into a single report format.

Key messages:

Vaccine exposure:

Vaccine exposure rates for all ages have **increased** from **18.02 in week 46** to **18.63 in week 47**.

Practice types:
Enhanced passive practices gave vaccinated patients a card to prompt reporting; Electronic Health Record (EHR) data mining practices have findings reported from routine data.

Possible adverse events in the vaccinated population by Enhance passive and EHR data mining practices (per 100,000 patients):

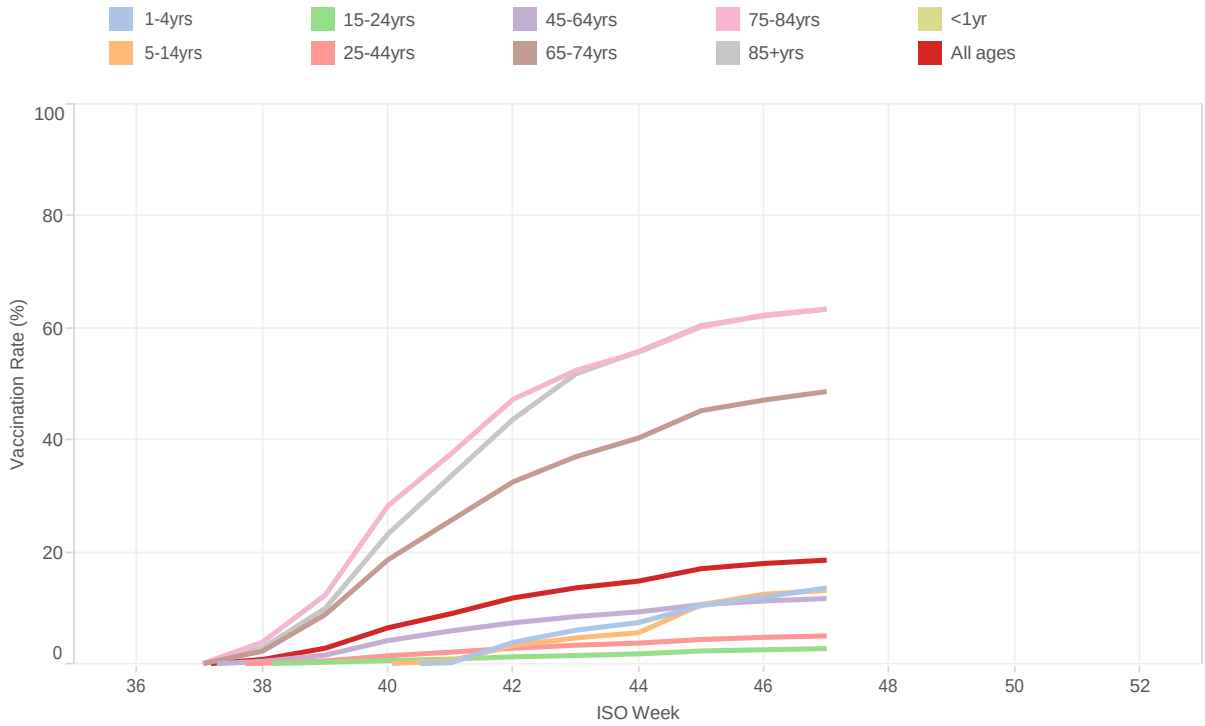
- **Fever/Pyrexia :** Enhanced passive rate was **456.6** in week 47 compared with **0.0** in week 46. EHR data mining rate was **952.4** in week 47 compared with **407.6** in week 46.
- **Gastrointestinal :** Enhanced passive rate was **228.3** in week 47 compared with **0.0** in week 46. EHR data mining rate was **714.3** in week 47 compared with **0.0** in week 46.
- **General symptoms :** Enhanced passive rate was **0.0** in week 47 compared with **0.0** in week 46. EHR data mining rate was **119.0** in week 47 compared with **339.7** in week 46.
- **Local symptoms :** Enhanced passive rate was **0.0** in week 47 compared with **0.0** in week 46. EHR data mining rate was **0.0** in week 47 compared with **0.0** in week 46.
- **Musculoskeletal :** Enhanced passive rate was **456.6** in week 47 compared with **188.7** in week 46. EHR data mining rate was **714.3** in week 47 compared with **475.5** in week 46.
- **Neurological :** Enhanced passive rate was **0.0** in week 47 compared with **94.3** in week 46. EHR data mining rate was **238.1** in week 47 compared with **203.8** in week 46.
- **Rash :** Enhanced passive rate was **0.0** in week 47 compared with **94.3** in week 46. EHR data mining rate was **595.2** in week 47 compared with **135.9** in week 46.
- **Respiratory/Miscellaneous :** Enhanced passive rate was **456.6** in week 47 compared with **94.3** in week 46. EHR data mining rate was 1309.5 **in week 47** compared with **815.2** in week 46.
- **Sensitivity/anaphylaxis :** Enhanced passive rate was **228.3** in week 47 compared with **0.0** in week 46. EHR data mining rate was **0.0** in week 47 compared with **67.9** in week 46.

Comment:

The proportion of the practice population vaccinated continued to increase this week. The most common possible adverse event categories this week were respiratory/miscellaneous, and fever/pyrexia.

Influenza vaccine exposure rates

- **Cumulative vaccine exposure rates: All age groups, 2015 ***



* The vaccination exposure rates are a percentage of all registered patients in the pilot practices.

- **Cumulative vaccine exposure rates: All age groups, by vaccine brand, 2015 ***

	GSK vaccine	Non-GSK vaccine
<1yr		
1-4yrs	9.17	14.57
5-14yrs	3.53	15.35
15-24yrs	3.17	2.77
25-44yrs	5.09	5.12
45-64yrs	12.85	11.52
65-74yrs	57.17	46.46
75-84yrs	77.51	59.25
85+yrs	74.40	60.26
All ages	22.49	17.72

* The GSK vaccine rates are based on the vaccine exposure rates in 2 out of 9 of the pilot practices.

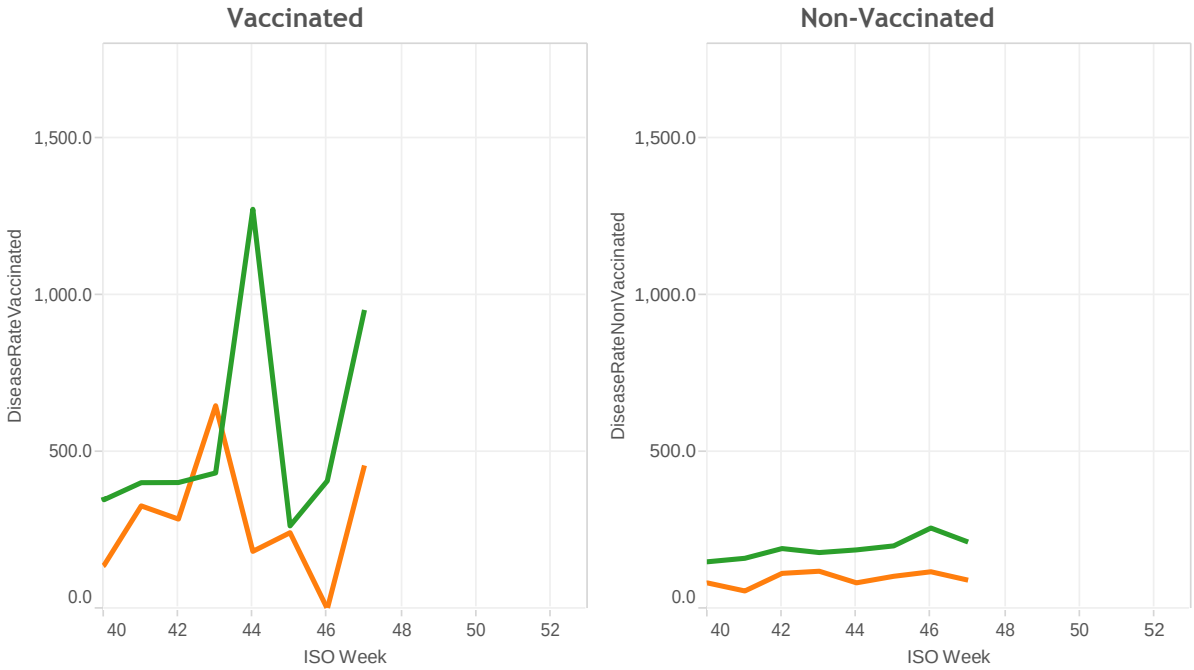
- **Key denominators**

	Registered Patients	Vaccinated Patients	Vaccination Rate
Non-GSK vaccine	64,871	11,494	17.72
GSK vaccine	15,297	3,440	22.49
Grand Total	80,955	14,934	18.63

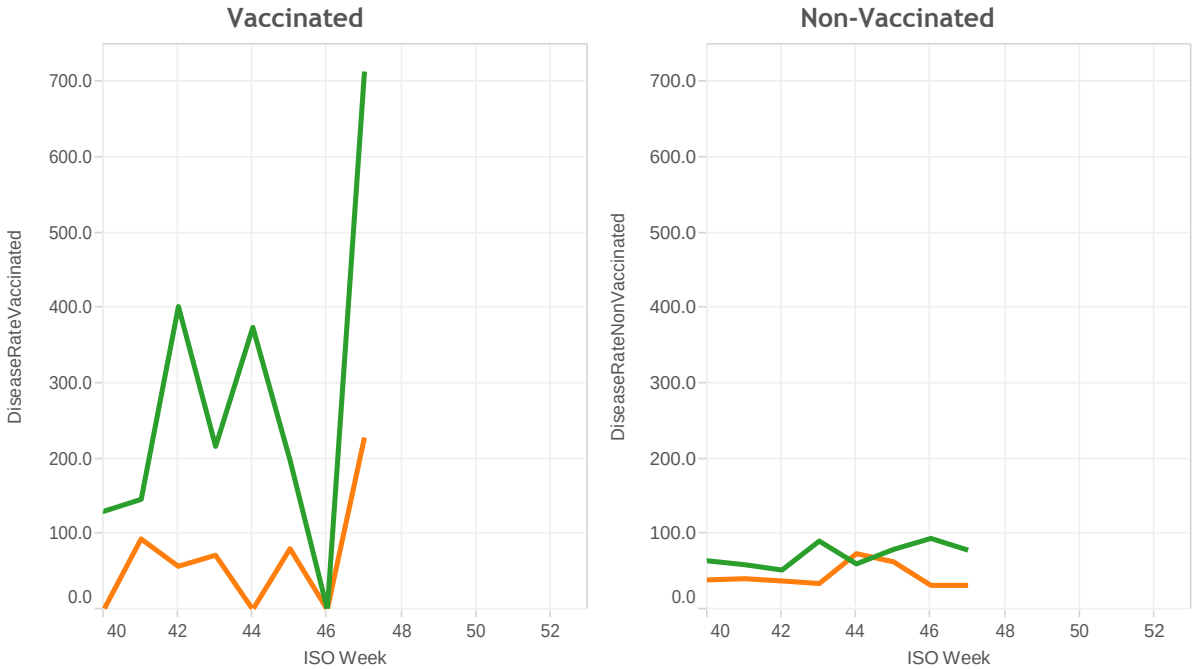
	Registered Patients	Vaccinated Patients	Vaccination Rate
EHR data mining	51,366	8,118	15.80
Enhanced passive	28,802	6,816	23.67
Grand Total	80,955	14,934	18.63

Possible adverse event rates by EMA surveillance condition

- **Fever/Pyrexia by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

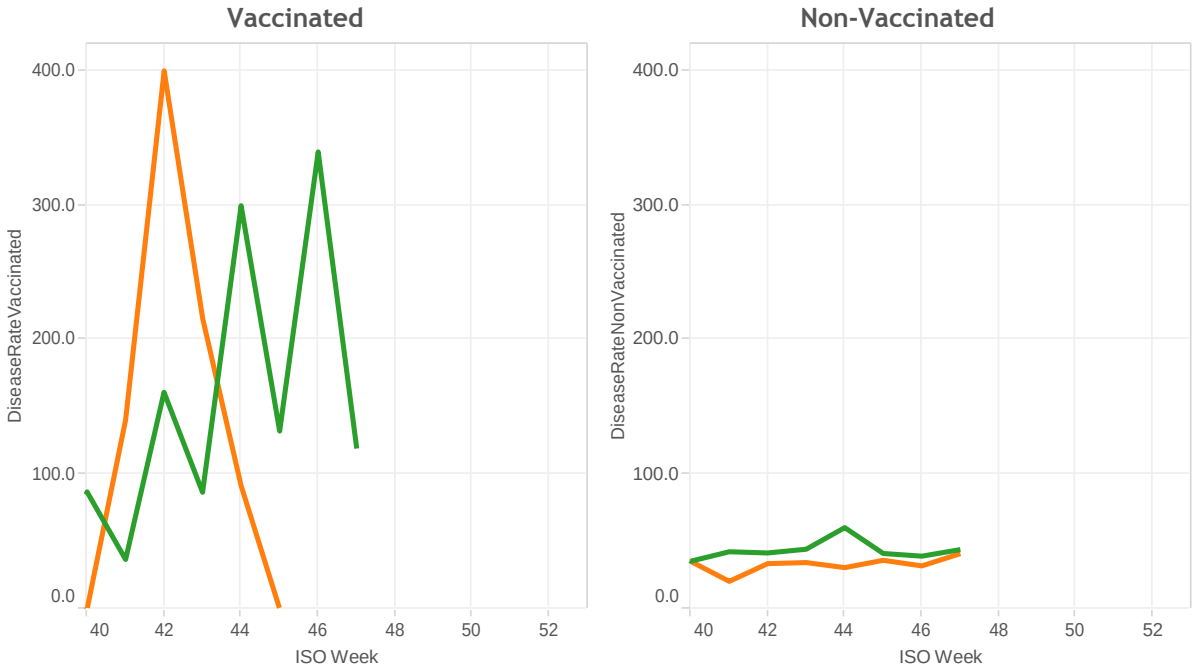


- **Gastrointestinal by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

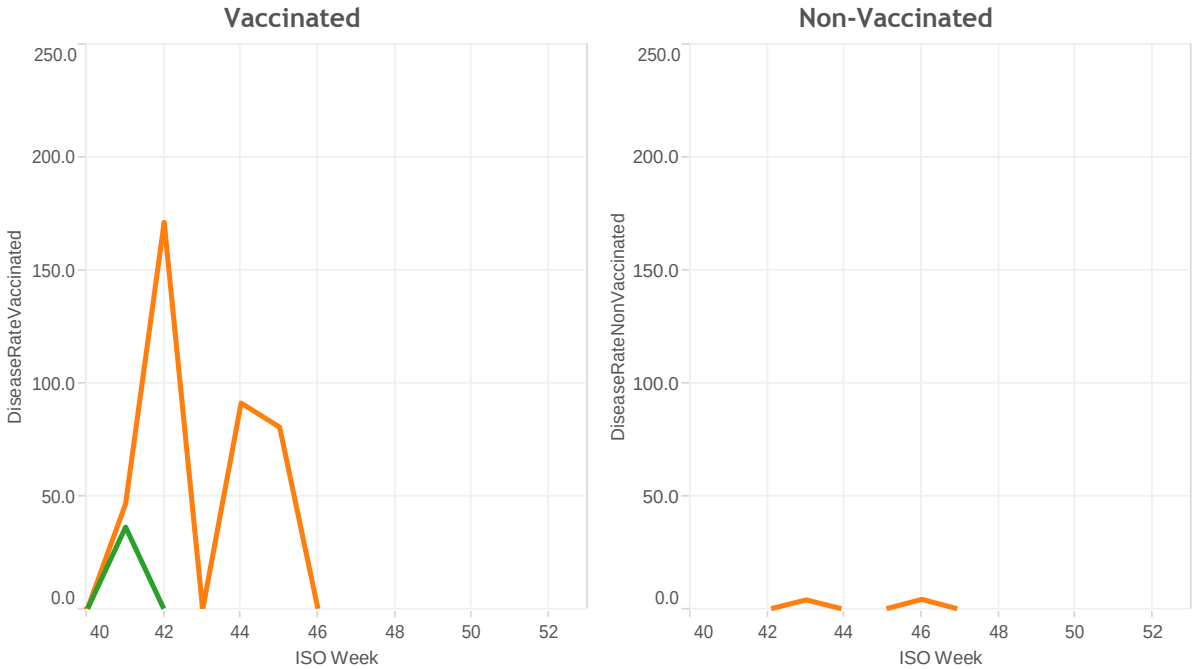


Possible adverse event rates by EMA surveillance condition

- **General non-specific symptoms by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

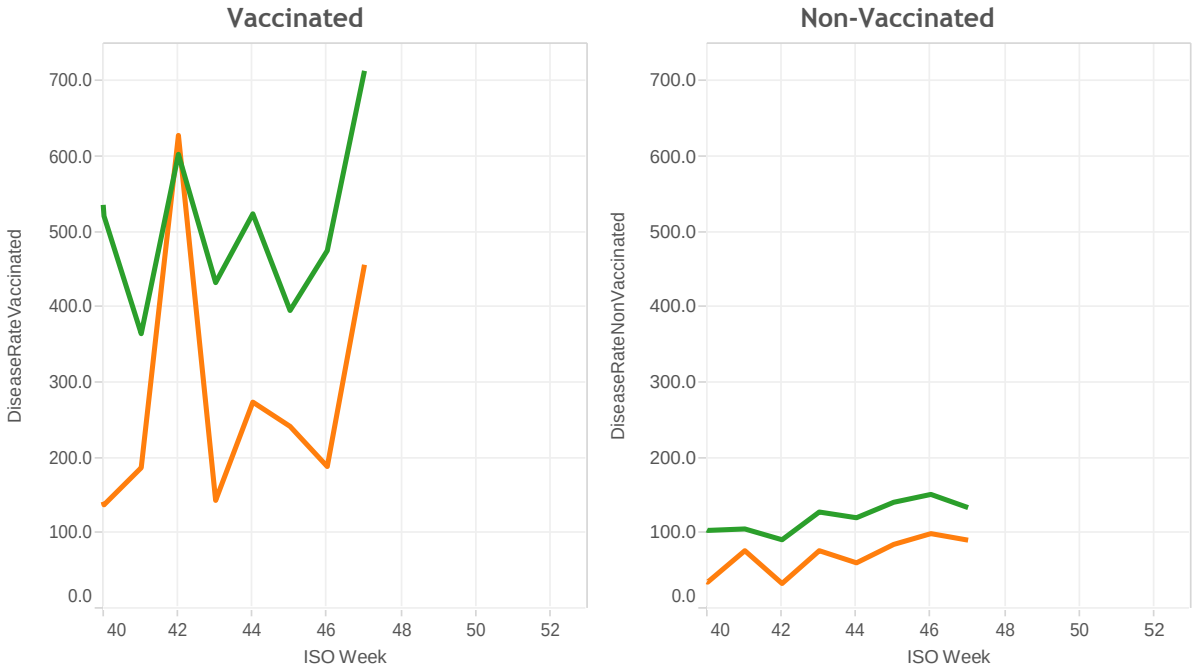


- **Local symptoms by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

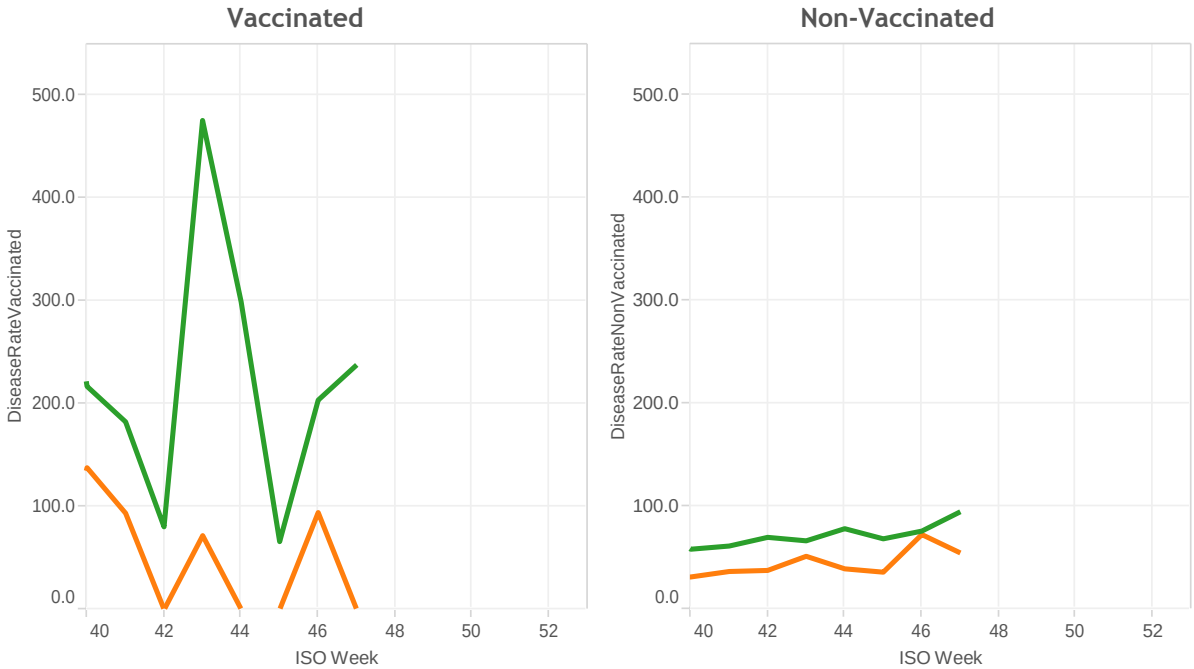


Possible adverse event rates by EMA surveillance condition

- **Musculoskeletal by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

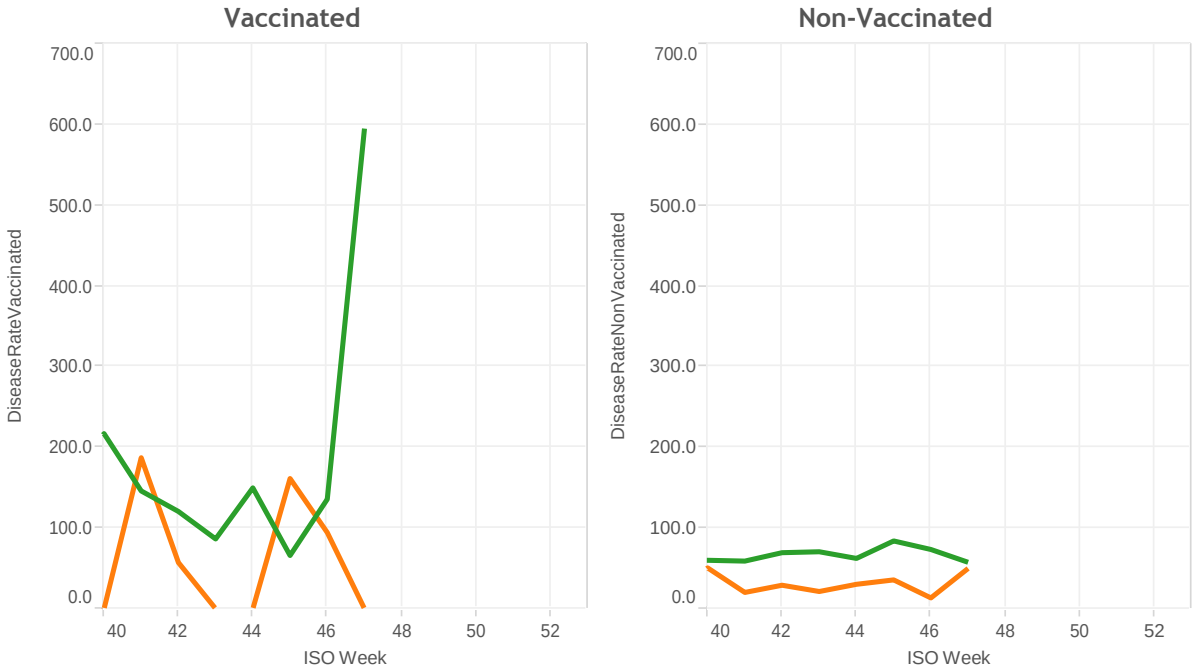


- **Neurological by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

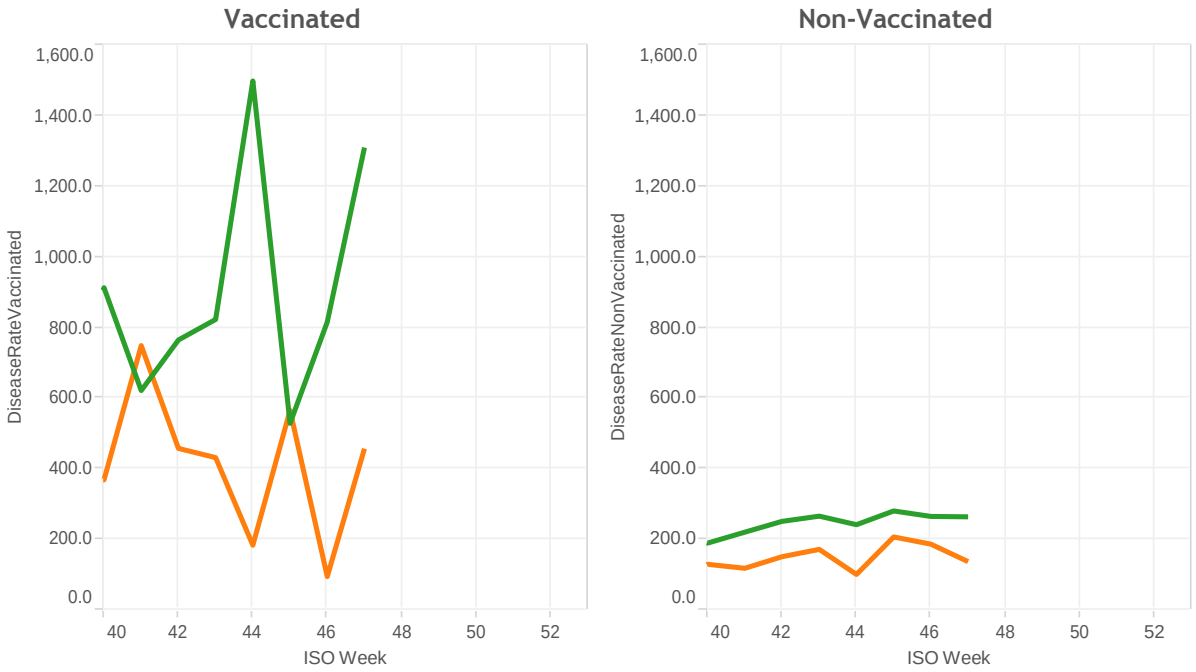


Possible adverse event rates by EMA surveillance condition

- **Rash by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**



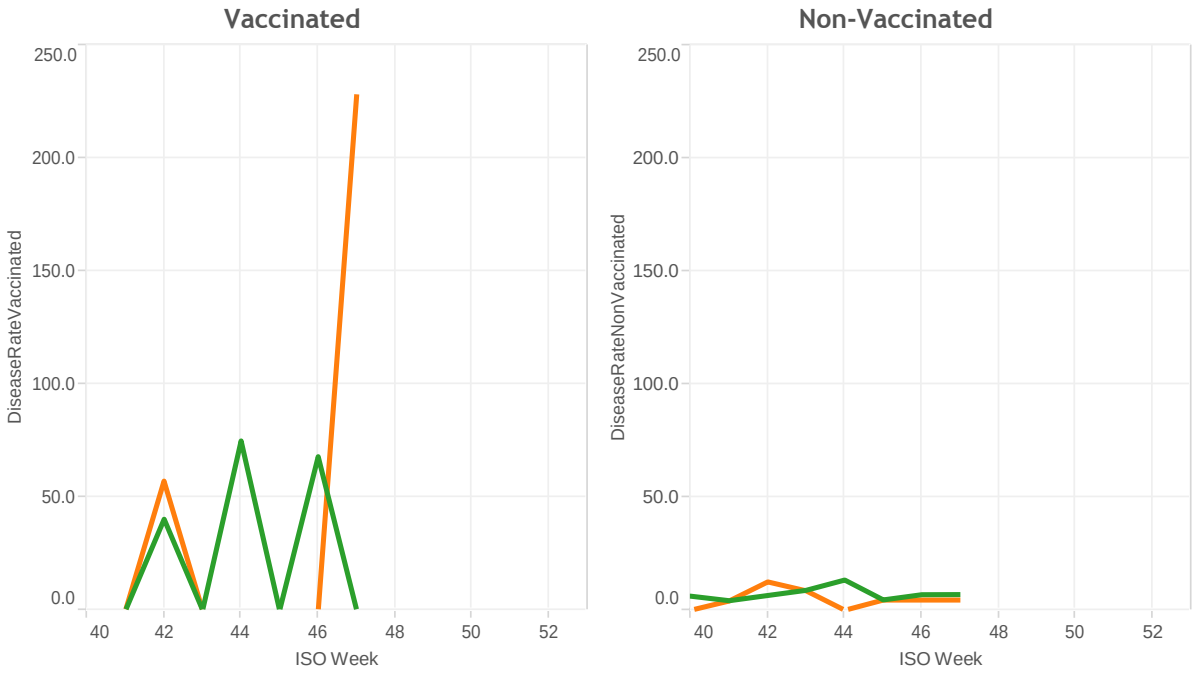
- **Respiratory/Miscellaneous by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**



Possible adverse event rates by EMA surveillance condition, and weekly summary by vaccine brand

EHR data mining Enhanced passive

- **Sensitivity/Anaphylaxis by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**



- **Possible adverse events by GSK or non-GSK vaccines: Incidence rates per 100,000, 2015 ****

Week number		47	46	45	44	43
Week beginning		16/11/2015	09/11/2015	02/11/2015	26/10/2015	19/10/2015
Week ending		22/11/2015	15/11/2015	08/11/2015	01/11/2015	25/10/2015
Fever/Pyrexia	GSK	621.1	0.0	511.1	148.8	669.3
	Non-GSK	836.8	303.3	184.6	1,024.5	473.9
Gastrointestinal	GSK	0.0	0.0	170.4	0.0	0.0
	Non-GSK	732.2	0.0	138.4	284.6	203.1
General symptoms	GSK	0.0	0.0	0.0	0.0	267.7
	Non-GSK	104.6	252.8	92.3	284.6	101.6
Local symptoms	GSK	0.0	0.0	170.4	148.8	0.0
	Non-GSK	0.0	0.0	0.0	0.0	0.0
Musculoskeletal	GSK	621.1	361.0	511.1	446.4	267.7
	Non-GSK	627.6	353.9	276.9	398.4	338.5
Neurological	GSK	0.0	180.5	0.0	0.0	133.9
	Non-GSK	209.2	151.7	46.1	227.7	372.4
Rash	GSK	0.0	180.5	340.7	0.0	0.0
	Non-GSK	523.0	101.1	46.1	113.8	67.7
Respiratory/Miscellaneous	GSK	621.1	180.5	511.1	148.8	535.5
	Non-GSK	1,150.6	606.7	553.8	1,195.2	710.9
Sensitivity/Anaphylaxis	GSK	0.0	0.0	0.0	0.0	0.0
	Non-GSK	104.6	50.6	0.0	56.9	0.0

0.0 200.0 400.0

** It must be noted that the two GSK practices are both conducting enhanced passive surveillance.

Weekly summary of possible adverse event rates by EMA surveillance condition and practice type

- **Possible adverse events by Enhanced passive or EHR data mining practices: Incidence rates per 100,000 and count of episodes, 2015**

Week number		47		46		45		44		43	
Week beginning		16/11/2015		09/11/2015		02/11/2015		26/10/2015		19/10/2015	
Week ending		22/11/2015		15/11/2015		08/11/2015		01/11/2015		25/10/2015	
		Episodes	Rate	Episodes	Rate	Episodes	Rate	Episodes	Rate	Episodes	Rate
Fever/Pyrexia	EHR data mining	8	952.4	6	407.6	4	264.0	17	1,273.4	10	432.9
	Enhanced passive	2	456.6	0	0.0	3	242.1	2	182.8	9	647.0
Gastrointestinal	EHR data mining	6	714.3	0	0.0	3	198.0	5	374.5	5	216.5
	Enhanced passive	1	228.3	0	0.0	1	80.7	0	0.0	1	71.9
General symptoms	EHR data mining	1	119.0	5	339.7	2	132.0	4	299.6	2	86.6
	Enhanced passive	0	0.0	0	0.0	0	0.0	1	91.4	3	215.7
Local symptoms	EHR data mining	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Enhanced passive	0	0.0	0	0.0	1	80.7	1	91.4	0	0.0
Musculoskeletal	EHR data mining	6	714.3	7	475.5	6	396.0	7	524.3	10	432.9
	Enhanced passive	2	456.6	2	188.7	3	242.1	3	274.2	2	143.8
Neurological	EHR data mining	2	238.1	3	203.8	1	66.0	4	299.6	11	476.2
	Enhanced passive	0	0.0	1	94.3	0	0.0	0	0.0	1	71.9
Rash	EHR data mining	5	595.2	2	135.9	1	66.0	2	149.8	2	86.6
	Enhanced passive	0	0.0	1	94.3	2	161.4	0	0.0	0	0.0
Respiratory/ Miscellaneous	EHR data mining	11	1,309.5	12	815.2	8	528.1	20	1,498.1	19	822.5
	Enhanced passive	2	456.6	1	94.3	7	565.0	2	182.8	6	431.3
Sensitivity/ Anaphylaxis	EHR data mining	0	0.0	1	67.9	0	0.0	1	74.9	0	0.0
	Enhanced passive	1	228.3	0	0.0	0	0.0	0	0.0	0	0.0

Registered Patients	EHR data mining	51,366	51,236	51,151	51,023	50,932
	Enhanced passive	28,802	28,703	28,633	28,551	28,486
Vaccinated Patients	EHR data mining	8,118	7,748	7,262	6,262	5,734
	Enhanced passive	6,816	6,656	6,366	5,583	5,120
Registered Patients	**Total**	80,955	80,936	80,911	80,831	80,796
Vaccinated Patients	**Total**	14,934	14,404	13,628	11,845	10,854

Further information:

Post-authorisation safety surveillance pilot study

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We are assessing adverse event of interest (AEI) frequencies among subjects who have received the influenza vaccine, using routinely collected data in nine primary care practices. AEIs up to 14 days from the date of vaccination are included for vaccinated patients. We are also providing the rate of these events in non-vaccinated patients, to assess background rates and trends. Where these conditions are found in non-vaccinated subjects we call them illness-disease episodes (IDE).

Three practices are taking part in the enhanced passive surveillance sub-study, where a reporting card has been given to vaccinated patients to return to the practices.

This report shows the weekly data flow capturing vaccine coverage, and proportions of patients reporting possible AEIs within the EMA's surveillance condition categories. The results of this pilot will be used to assess whether the data collected in the study meet the requirements of enhanced safety surveillance as stipulated in the interim guidance issued by EMA in April 2014.

This pilot study has received [redacted] approval (REF: 15/LO/1254).

How rates of possible adverse events are calculated

Denominator: The vaccinated denominator are all registered patients in the participating practices who have received the seasonal influenza vaccine in the preceding 2 weeks. The non-vaccinated denominator are all registered patients who have not received the seasonal influenza vaccine to date.

Numerator: The numerator for the vaccinated patients is the number of possible adverse events occurring during the current study week, which happened within a 14-day window after the patient received the seasonal influenza vaccine. The numerator for the non-vaccinated patients is the number of possible adverse events occurring during the study week, for non-vaccinated patients.

Detailed numerators and denominators for the vaccinated patients are stated in graph (L), page 8.

Vaccinated and non-vaccinated comparisons

This pilot study is not designed to provide a formal comparison of the two groups, but the rates of possible AEIs in the non-vaccinated population are included to provide a crude background rate. In future years, once more data has been collected, a more accurate background rate could be established using a 5 year average.

Timeliness of the data

In routine primary care data, the date of recording may differ from the date of the event. Sometimes GPs may add an entry to the patient's record several weeks after the date of the event. Usually, this lag in recording would not be greater than 6 weeks. Therefore, it is expected that each week there may be a small variation in the AEI rates from previous weeks, as new data is recorded.

Further information:

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Data are held on secure servers at the Section of Clinical Medicine and Ageing at the [redacted] Both Apollo and the [redacted] are registered and compliant with the Data Protection Act and fully compliant with all relevant HSCIC and NHS data information governance best practice.

For further information, please contact:

Professor [redacted]
[redacted]

[redacted]

[redacted]

Post-authorisation safety study of influenza vaccine

Key Statistics:

Week Number/Year…….48/2015
Week Starting - Ending……..…23/11/2015 - 29/11/2015
No. of Practices……9
Population…….80977 (15448 vaccinated)

Post-authorisation safety study:

The European Medicines Agency (EMA) has set out new requirements for influenza vaccine safety surveillance that all Marketing Authorisation Holders (MAHs) providing vaccines in the EU must address. This pilot, funded by Glaxo-SmithKline and conducted by the [redacted] explores the use of routinely collected data in the UK to provide timely and relevant information on influenza vaccine safety.

UK primary care is highly computerised, though the major suppliers have different data models, coding systems, and methods of data access. This pilot study demonstrates the feasibility of drawing together the heterogeneous data from different brands of computer system into a single report format.

Key messages:

Vaccine exposure:

Vaccine exposure rates for all ages have **increased** from **18.63 in week 47** to **19.22 in week 48**.

Practice types:
Enhanced passive practices gave vaccinated patients a card to prompt reporting; Electronic Health Record (EHR) data mining practices have findings reported from routine data.

Possible adverse events in the vaccinated population by Enhanced passive and EHR data mining practices (per 100,000 patients):

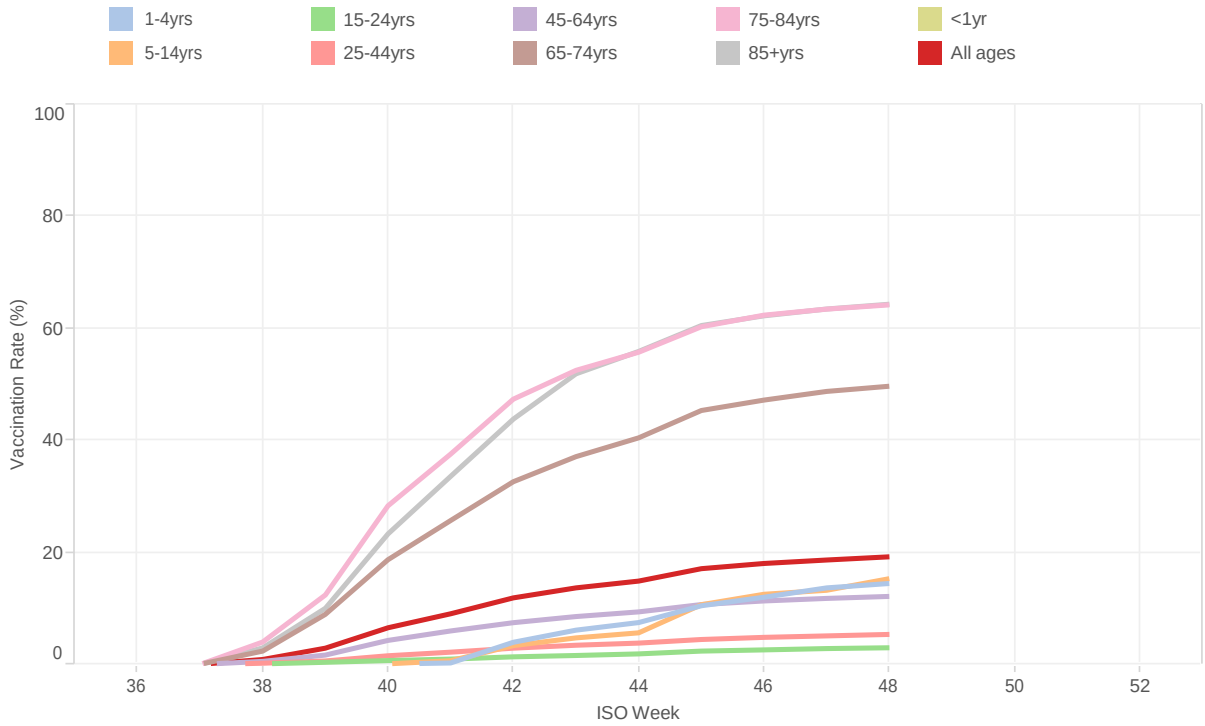
- **Fever/Pyrexia :** Enhanced passive rate was **456.6** in week 47 compared with **0.0** in week 48. EHR data mining rate was **952.4** in week 47 compared with **1170.6 in week 48.**
- **Gastrointestinal :** Enhanced passive rate was **228.3** in week 47 compared with **0.0** in week 48. EHR data mining rate was **714.3** in week 47 compared with **167.2** in week 48.
- **General symptoms :** Enhanced passive rate was **0.0** in week 47 compared with **0.0** in week 48. EHR data mining rate was **119.0** in week 47 compared with **0.0** in week 48.
- **Local symptoms :** Enhanced passive rate was **0.0** in week 47 compared with **0.0** in week 48. EHR data mining rate was **0.0** in week 47 compared with **0.0** in week 48.
- **Musculoskeletal :** Enhanced passive was **456.6** in week 47 compared with **0.0** in week 48. EHR data mining rate was **714.3** in week 47 compared with **668.9** in week 48.
- **Neurological :** Enhanced passive rate was **0.0** in week 47 compared with **0.0** in week 48. EHR data mining rate was **238.1** in week 47 compared with **501.7** in week 48.
- **Rash :** Enhanced passive rate was **0.0** in week 47 compared with **0.0** in week 48. EHR data mining rate was **595.2** in week 47 compared with **0.0** in week 48.
- **Respiratory/Miscellaneous :** Enhanced passive rate was **456.6** in week 47 compared with **726.4** in week 48. EHR data mining rate was **1309.5** in week 47 compared with **668.9** in week 48.
- **Sensitivity/anaphylaxis :** Enhanced passive rate was **228.3** in week 47 compared with **0.0** in week 48. EHR data mining rate was **0.0** in week 47 compared with **0.0** in week 48.

Comment:

The proportion of the practice population vaccinated continued to increase this week. The most common possible adverse event categories this week were respiratory/miscellaneous, and fever/pyrexia.

Influenza vaccine exposure rates

- **Cumulative vaccine exposure rates: All age groups, 2015 ***



* The vaccination exposure rates are a percentage of all registered patients in the pilot practices.

- **Cumulative vaccine exposure rates: All age groups, by vaccine brand, 2015 ***

	GSK vaccine	Non-GSK vaccine
<1yr		
1-4yrs	9.68	15.42
5-14yrs	3.59	17.87
15-24yrs	3.75	2.84
25-44yrs	5.25	5.40
45-64yrs	13.18	11.90
65-74yrs	58.18	47.39
75-84yrs	78.29	60.01
85+yrs	75.68	61.03
All ages	22.91	18.35

* The GSK vaccine rates are based on the vaccine exposure rates in 2 out of 9 of the pilot practices.

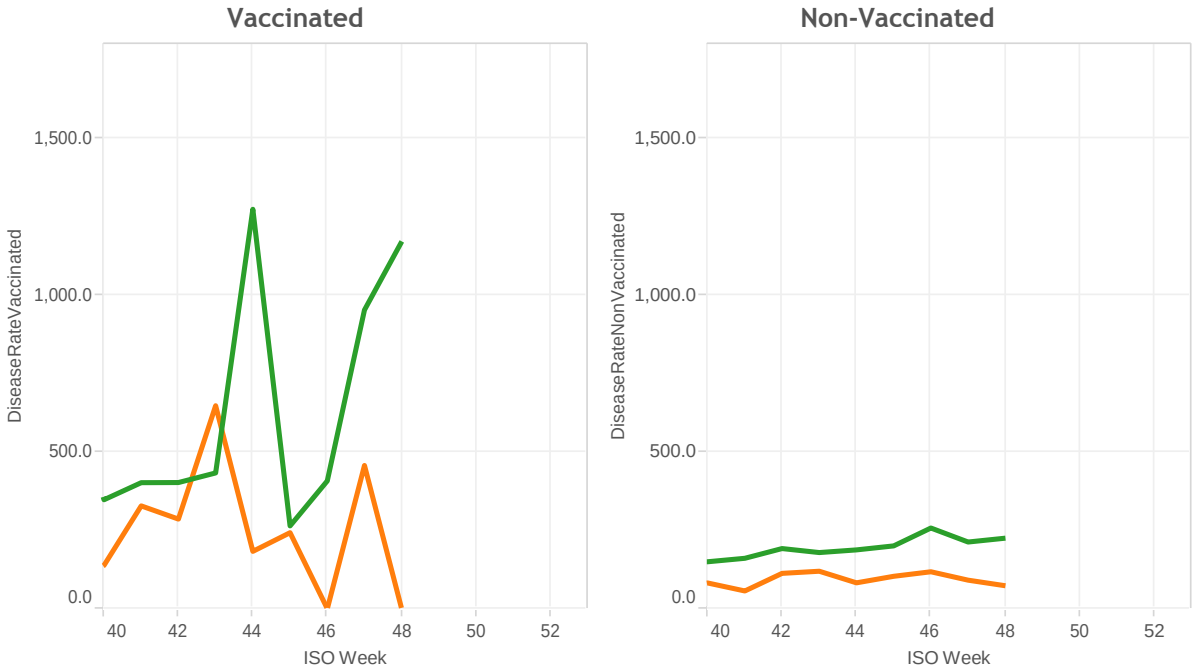
- **Key denominators**

	Registered Patients	Vaccinated Patients	Vaccination Rate
Non-GSK vaccine	65,026	11,934	18.35
GSK vaccine	15,336	3,514	22.91
Grand Total	80,977	15,448	19.22

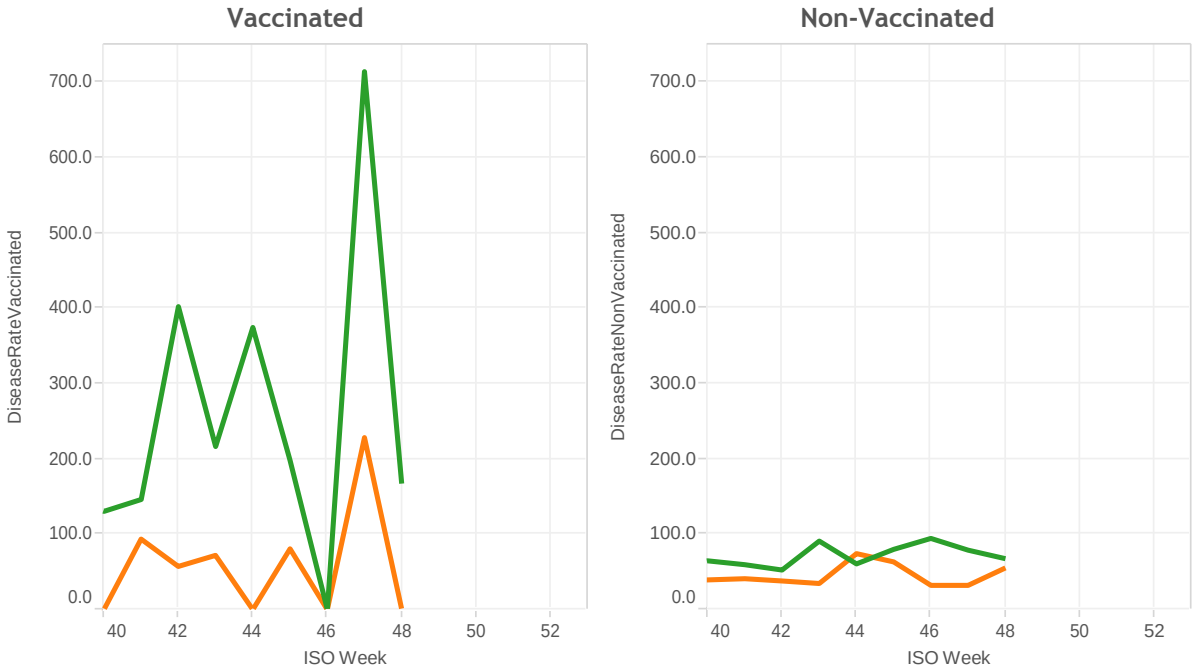
	Registered Patients	Vaccinated Patients	Vaccination Rate
EHR data mining	51,485	8,366	16.25
Enhanced passive	28,877	7,082	24.52
Grand Total	80,977	15,448	19.22

Possible adverse event rates by EMA surveillance condition

- **Fever/Pyrexia by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

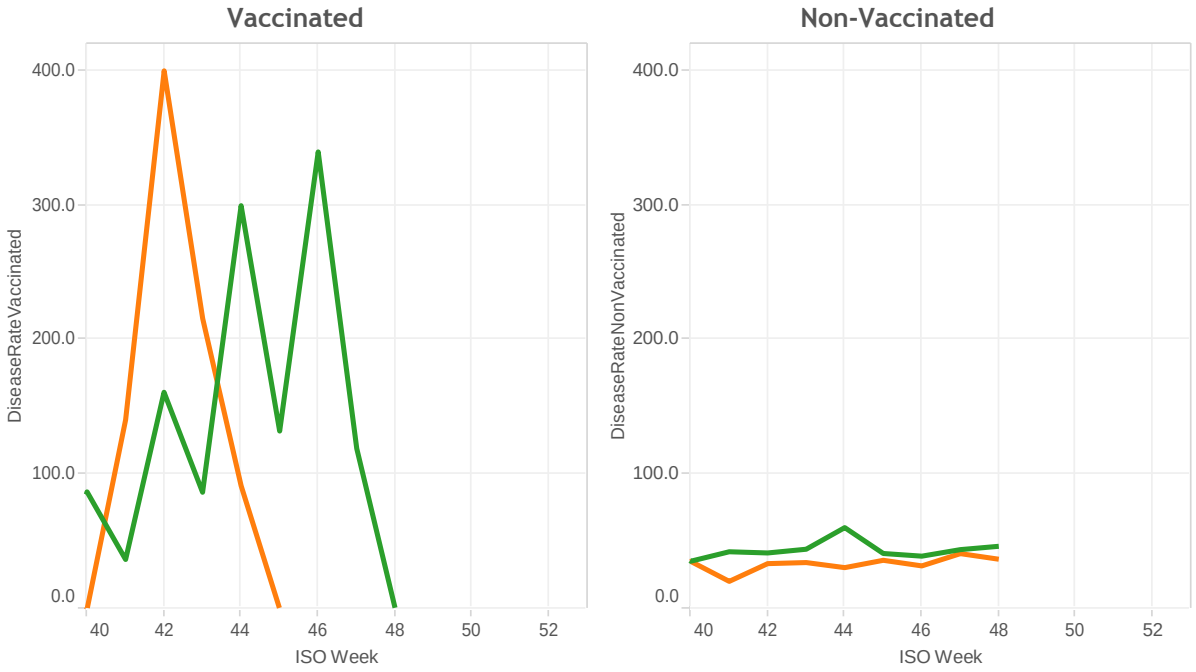


- **Gastrointestinal by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

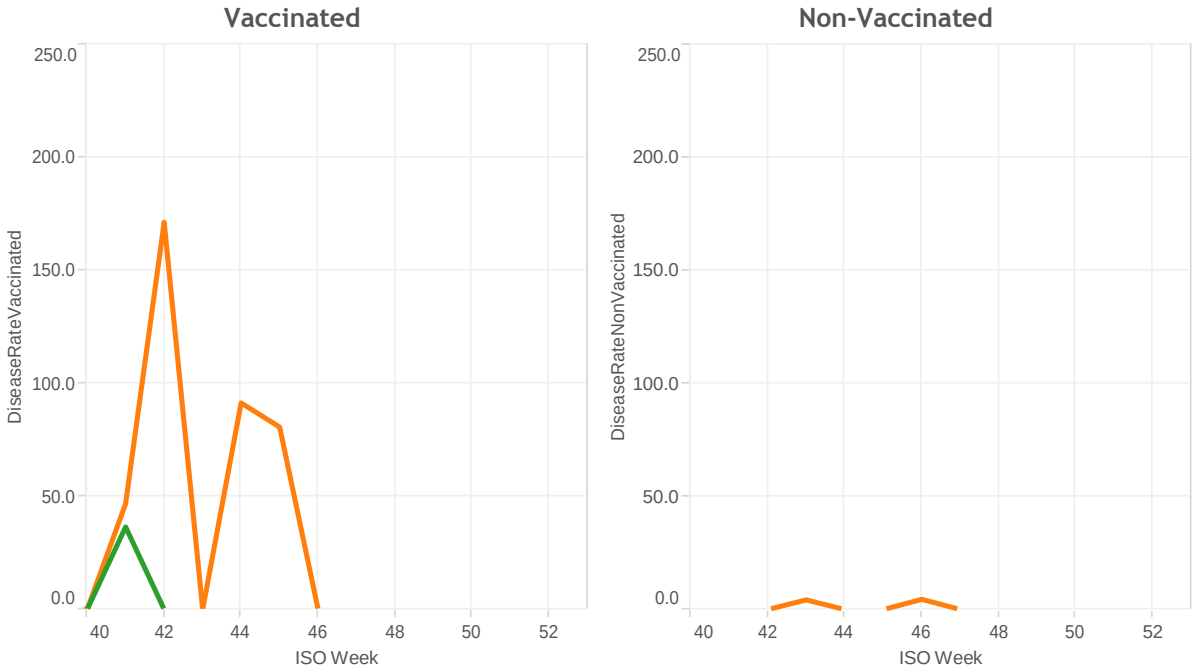


Possible adverse event rates by EMA surveillance condition

- **General non-specific symptoms by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

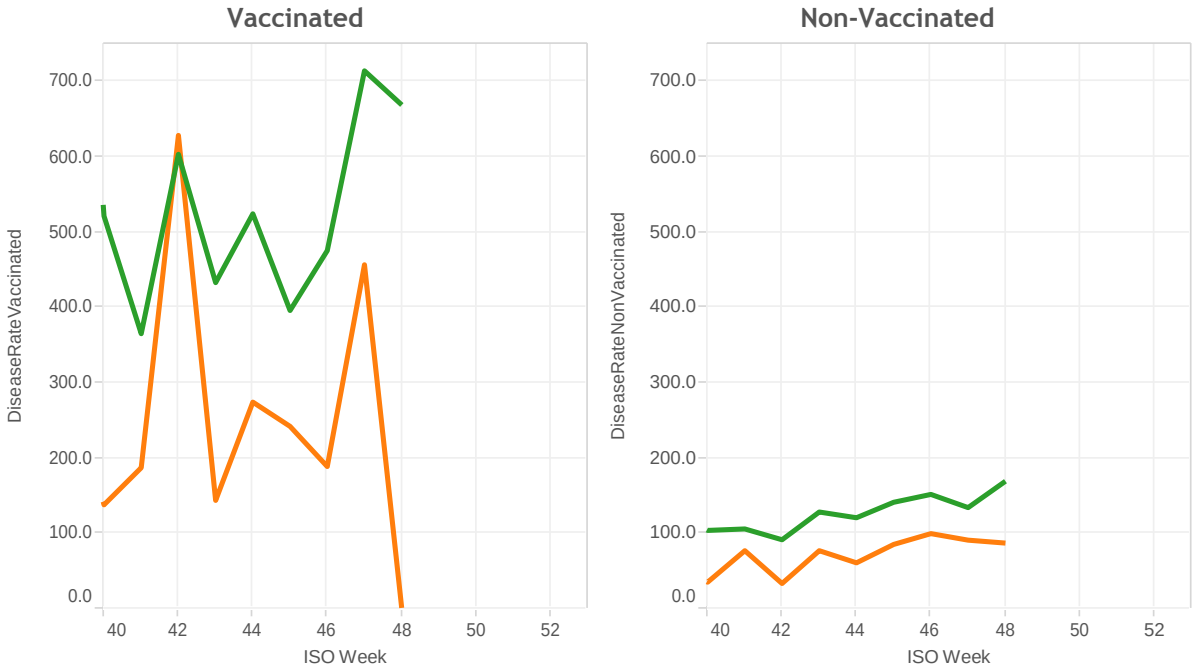


- **Local symptoms by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

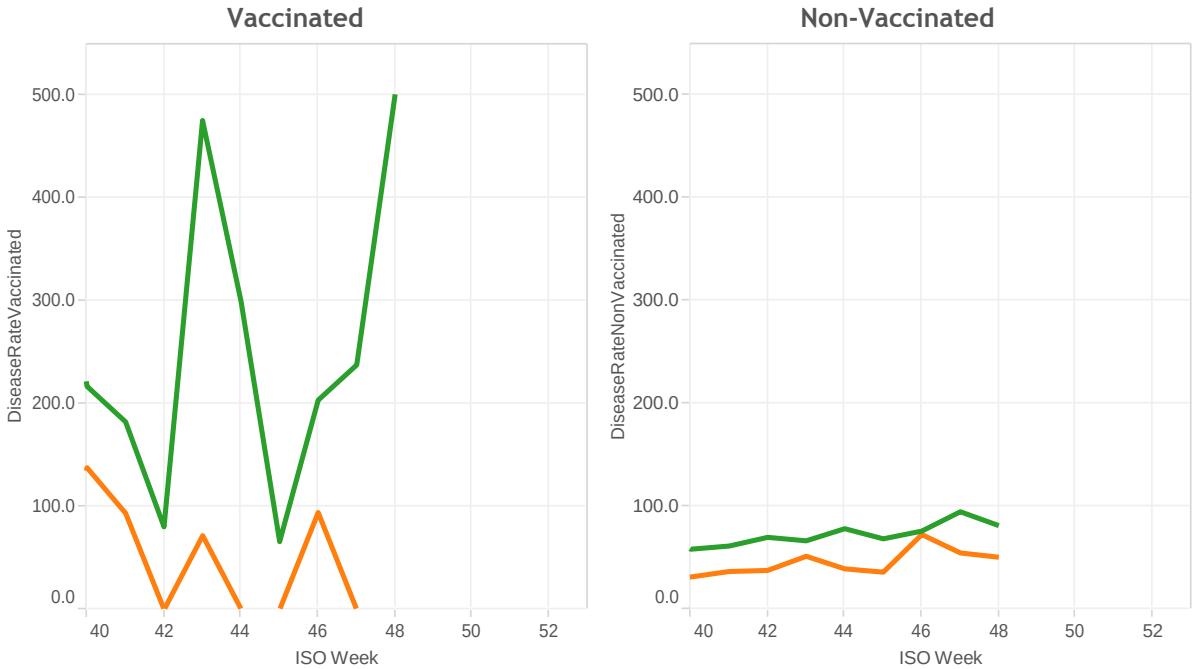


Possible adverse event rates by EMA surveillance condition

- **Musculoskeletal by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

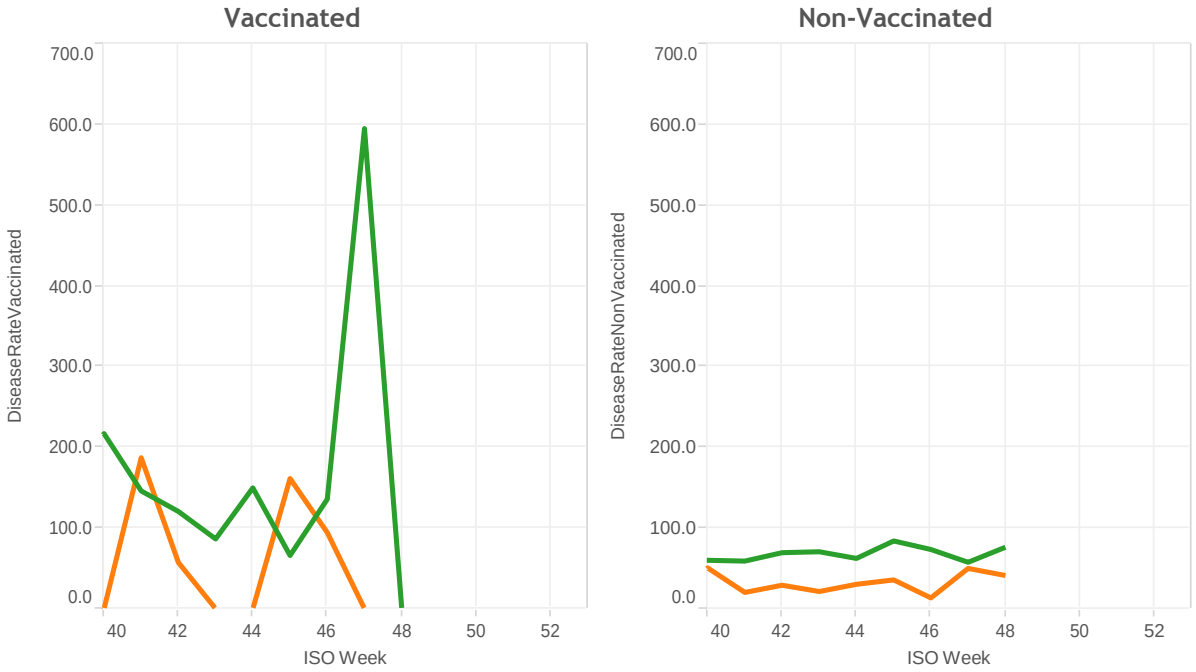


- **Neurological by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

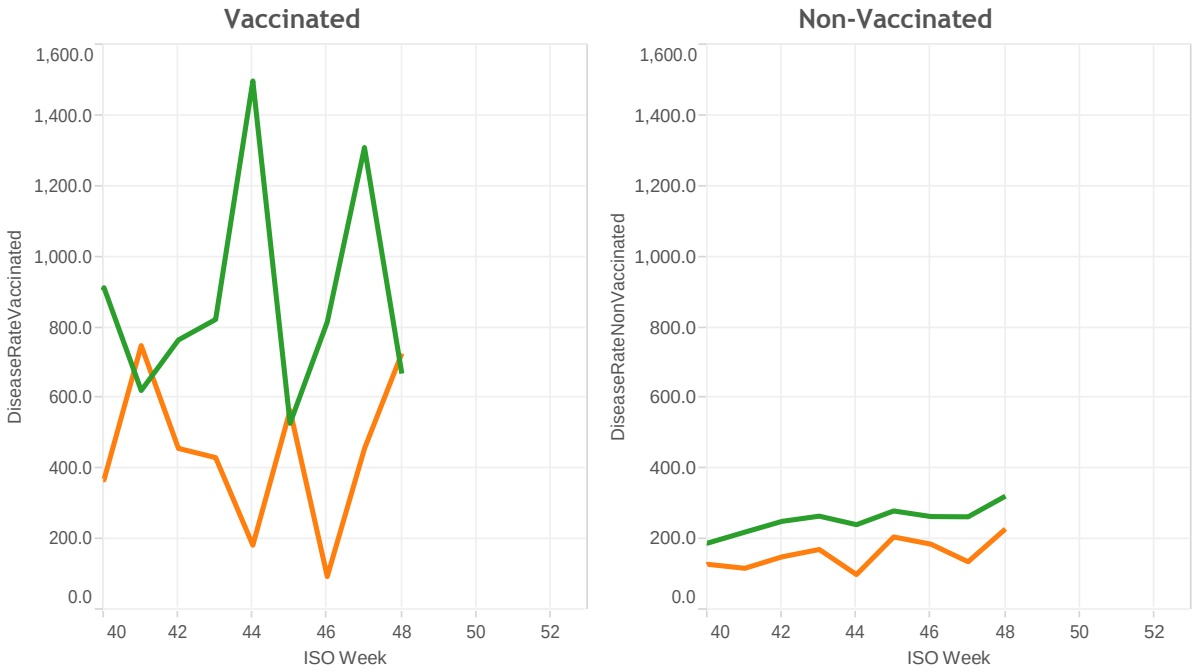


Possible adverse event rates by EMA surveillance condition

- **Rash by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

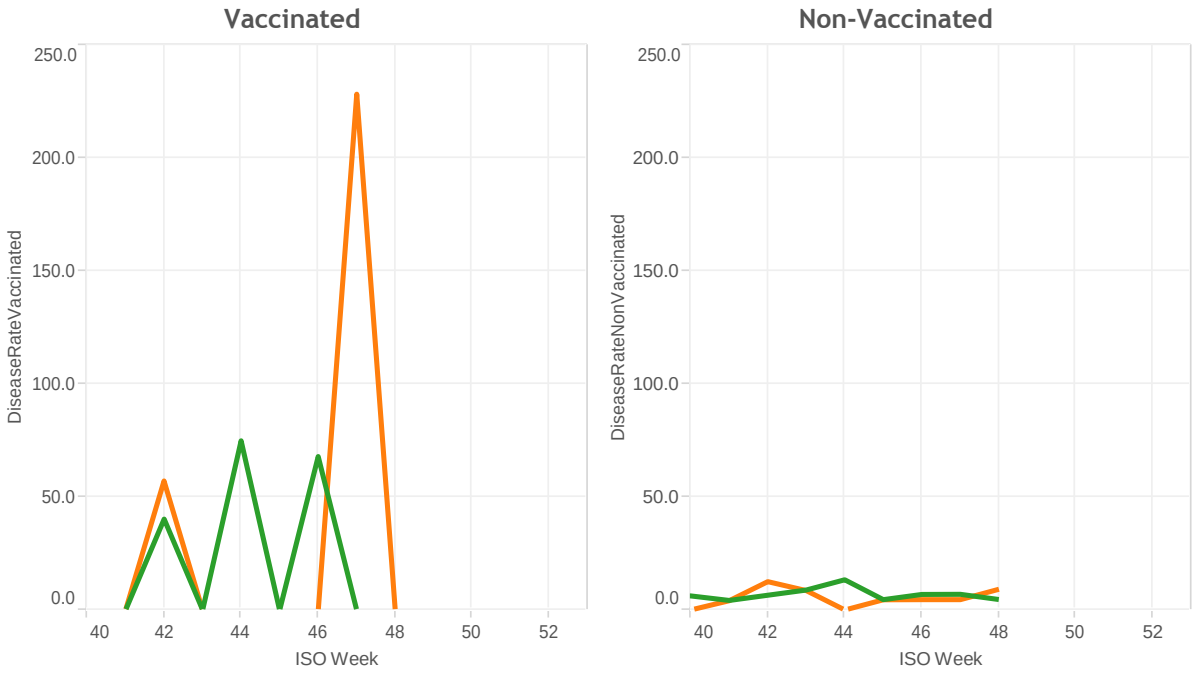


- **Respiratory/Miscellaneous by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**



Possible adverse event rates by EMA surveillance condition, and weekly summary by vaccine brand

- **Sensitivity/Anaphylaxis by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**



- **Possible adverse events by GSK or non-GSK vaccines: Incidence rates per 100,000, 2015 ****

Week number		48	47	46	45	44
Week beginning		23/11/2015	16/11/2015	09/11/2015	02/11/2015	26/10/2015
Week ending		29/11/2015	22/11/2015	15/11/2015	08/11/2015	01/11/2015
Fever/Pyrexia	GSK	0.0	621.1	0.0	511.1	148.8
	Non-GSK	829.4	836.8	303.3	184.6	1,024.5
Gastrointestinal	GSK	0.0	0.0	0.0	170.4	0.0
	Non-GSK	118.5	732.2	0.0	138.4	284.6
General symptoms	GSK	0.0	0.0	0.0	0.0	0.0
	Non-GSK	0.0	104.6	252.8	92.3	284.6
Local symptoms	GSK	0.0	0.0	0.0	170.4	148.8
	Non-GSK	0.0	0.0	0.0	0.0	0.0
Musculoskeletal	GSK	0.0	621.1	361.0	511.1	446.4
	Non-GSK	473.9	627.6	353.9	276.9	398.4
Neurological	GSK	0.0	0.0	180.5	0.0	0.0
	Non-GSK	355.5	209.2	151.7	46.1	227.7
Rash	GSK	0.0	0.0	180.5	340.7	0.0
	Non-GSK	0.0	523.0	101.1	46.1	113.8
Respiratory/Miscellaneous	GSK	1,796.4	621.1	180.5	511.1	148.8
	Non-GSK	473.9	1,150.6	606.7	553.8	1,195.2
Sensitivity/Anaphylaxis	GSK	0.0	0.0	0.0	0.0	0.0
	Non-GSK	0.0	104.6	50.6	0.0	56.9

0.0 200.0 400.0

** It must be noted that the two GSK practices are both conducting enhanced passive surveillance.

Weekly summary of possible adverse event rates by EMA surveillance condition and practice type

- **Possible adverse events by Enhanced passive or EHR data mining practices: Incidence rates per 100,000 and count of episodes, 2015**

Week number		48		47		46		45		44	
Week beginning		23/11/2015		16/11/2015		09/11/2015		02/11/2015		26/10/2015	
Week ending		29/11/2015		22/11/2015		15/11/2015		08/11/2015		01/11/2015	
		Episodes	Rate	Episodes	Rate	Episodes	Rate	Episodes	Rate	Episodes	Rate
Fever/Pyrexia	EHR data mining	7	1,170.6	8	952.4	6	407.6	4	264.0	17	1,273.4
	Enhanced passive	0	0.0	2	456.6	0	0.0	3	242.1	2	182.8
Gastrointestinal	EHR data mining	1	167.2	6	714.3	0	0.0	3	198.0	5	374.5
	Enhanced passive	0	0.0	1	228.3	0	0.0	1	80.7	0	0.0
General symptoms	EHR data mining	0	0.0	1	119.0	5	339.7	2	132.0	4	299.6
	Enhanced passive	0	0.0	0	0.0	0	0.0	0	0.0	1	91.4
Local symptoms	EHR data mining	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Enhanced passive	0	0.0	0	0.0	0	0.0	1	80.7	1	91.4
Musculoskeletal	EHR data mining	4	668.9	6	714.3	7	475.5	6	396.0	7	524.3
	Enhanced passive	0	0.0	2	456.6	2	188.7	3	242.1	3	274.2
Neurological	EHR data mining	3	501.7	2	238.1	3	203.8	1	66.0	4	299.6
	Enhanced passive	0	0.0	0	0.0	1	94.3	0	0.0	0	0.0
Rash	EHR data mining	0	0.0	5	595.2	2	135.9	1	66.0	2	149.8
	Enhanced passive	0	0.0	0	0.0	1	94.3	2	161.4	0	0.0
Respiratory/ Miscellaneous	EHR data mining	4	668.9	11	1,309.5	12	815.2	8	528.1	20	1,498.1
	Enhanced passive	3	726.4	2	456.6	1	94.3	7	565.0	2	182.8
Sensitivity/ Anaphylaxis	EHR data mining	0	0.0	0	0.0	1	67.9	0	0.0	1	74.9
	Enhanced passive	0	0.0	1	228.3	0	0.0	0	0.0	0	0.0

Registered Patients	EHR data mining	51,485	51,366	51,236	51,151	51,023
	Enhanced passive	28,877	28,802	28,703	28,633	28,551
Vaccinated Patients	EHR data mining	8,366	8,118	7,748	7,262	6,262
	Enhanced passive	7,082	6,816	6,656	6,366	5,583
Registered Patients	**Total**	80,977	80,955	80,936	80,911	80,831
Vaccinated Patients	**Total**	15,448	14,934	14,404	13,628	11,845

Further information:

Post-authorisation safety surveillance pilot study

The European Medicines Agency (EMA) has set out new requirements for influenza vaccine safety surveillance that all Marketing Authorisation Holders (MAHs) providing vaccines in the EU must address. This pilot, funded by GlaxoSmithKline and conducted by the [redacted] demonstrates the potential of routinely collected data in the UK to provide timely and relevant information on influenza vaccine safety.

We are assessing adverse event of interest (AEI) frequencies among subjects who have received the influenza vaccine, using routinely collected data in nine primary care practices. AEIs up to 14 days from the date of vaccination are included for vaccinated patients. We are also providing the rate of these events in non-vaccinated patients, to assess background rates and trends. Where these conditions are found in non-vaccinated subjects we call them illness-disease episodes (IDE).

Three practices are taking part in the enhanced passive surveillance sub-study, where a reporting card has been given to vaccinated patients to return to the practices.

This report shows the weekly data flow capturing vaccine coverage, and proportions of patients reporting possible AEIs within the EMA's surveillance condition categories. The results of this pilot will be used to assess whether the data collected in the study meet the requirements of enhanced safety surveillance as stipulated in the interim guidance issued by EMA in April 2014.

This pilot study has received [redacted] approval (REF: 15/LO/1254).

How rates of possible adverse events are calculated

Denominator: The vaccinated denominator are all registered patients in the participating practices who have received the seasonal influenza vaccine in the preceding 2 weeks. The non-vaccinated denominator are all registered patients who have not received the seasonal influenza vaccine to date.

Numerator: The numerator for the vaccinated patients is the number of possible adverse events occurring during the current study week, which happened within a 14-day window after the patient received the seasonal influenza vaccine. The numerator for the non-vaccinated patients is the number of possible adverse events occurring during the study week, for non-vaccinated patients.

Detailed numerators and denominators for the vaccinated patients are stated in graph (L), page 8.

Vaccinated and non-vaccinated comparisons

This pilot study is not designed to provide a formal comparison of the two groups, but the rates of possible AEIs in the non-vaccinated population are included to provide a crude background rate. In future years, once more data has been collected, a more accurate background rate could be established using a 5 year average.

Timeliness of the data

In routine primary care data, the date of recording may differ from the date of the event. Sometimes GPs may add an entry to the patient's record several weeks after the date of the event. Usually, this lag in recording would not be greater than 6 weeks. Therefore, it is expected that each week there may be a small variation in the AEI rates from previous weeks, as new data is recorded.

Further information:

Data extraction process and information governance

Data are extracted twice weekly from practice systems by Apollo Medical Systems on behalf of the [redacted] Patients who have withheld consent for data sharing are excluded from the extraction process. Data are pseudonymised as close to source as possible.

Data are held on secure servers at the Section of Clinical Medicine and Ageing at the [redacted] Both Apollo and the [redacted] are registered and compliant with the Data Protection Act and fully compliant with all relevant HSCIC and NHS data information governance best practice.

For further information, please contact:

Professor [redacted]
[redacted]

[redacted]

[redacted]

Post-authorisation safety study of influenza vaccine

Key Statistics:

Week Number/Year…….49/2015
Week Starting - Ending……..…30/11/2015 - 06/12/2015
No. of Practices……9
Population…….80635 (15791 vaccinated)

Post-authorisation safety study:

The European Medicines Agency (EMA) has set out new requirements for influenza vaccine safety surveillance that all Marketing Authorisation Holders (MAHs) providing vaccines in the EU must address. This pilot, funded by Glaxo-SmithKline and conducted by the [redacted] explores the use of routinely collected data in the UK to provide timely and relevant information on influenza vaccine safety.

UK primary care is highly computerised, though the major suppliers have different data models, coding systems, and methods of data access. This pilot study demonstrates the feasibility of drawing together the heterogeneous data from different brands of computer system into a single report format.

Key messages:

Vaccine exposure:

Vaccine exposure rates for all ages have **increased** from **19.22 in week 48** to **19.58 in week 49**.

Practice types:
Enhanced passive practices gave vaccinated patients a card to prompt reporting; Electronic Health Record (EHR) data mining practices have findings reported from routine data.

Possible adverse events in the vaccinated population by Enhanced passive and EHR data mining practices (per 100,000 patients):

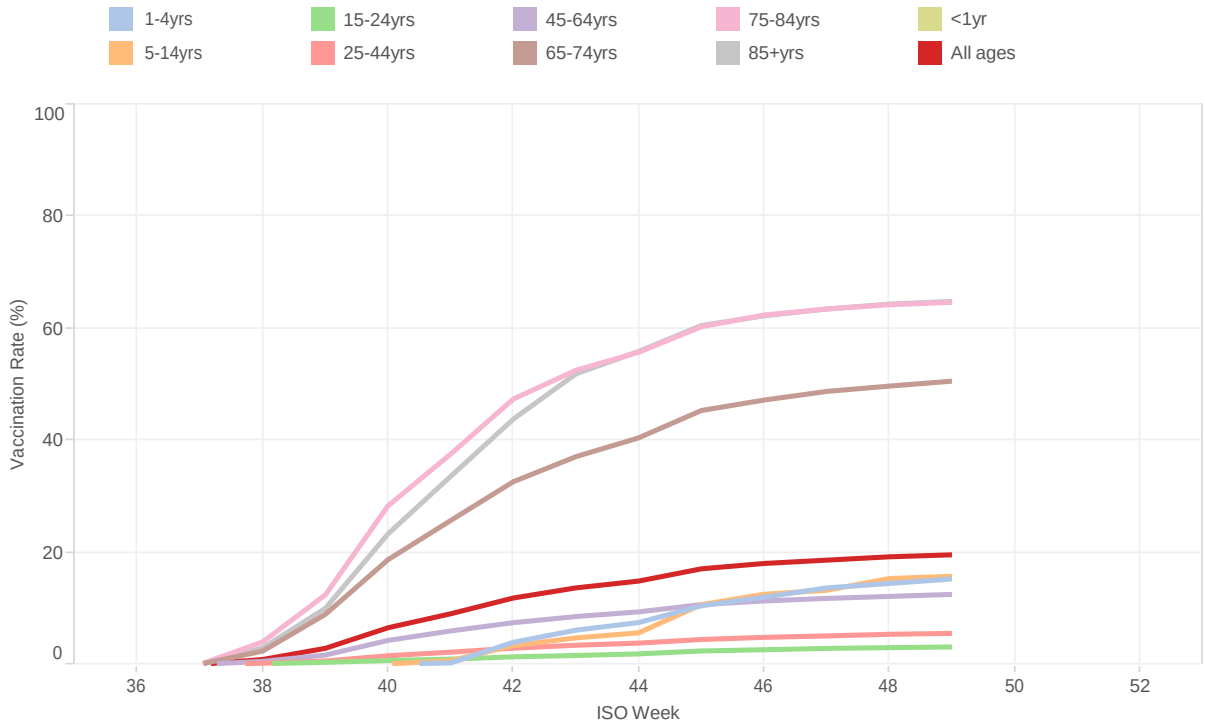
- **Fever/Pyrexia :** Enhanced passive rate was **0.0** in week 48 compared with **0.0** in week 49. EHR data mining rate was 1170.6 in week 48 compared with **1789.7** in week 49.
- **Gastrointestinal :** Enhanced passive rate was **0.0** in week 48 compared with **0.0** in week 49. EHR data mining rate was **167.2** in week 48 compared with **671.1** in week 49.
- **General symptoms :** Enhanced passive rate was **0.0** in week 48 compared with **0.0** in week 49. EHR data mining rate was **0.0** in week 48 compared with **0.0** in week 49.
- **Local symptoms :** Enhanced passive rate was **0.0** in week 48 compared with **0.0** in week 49. EHR data mining rate was **0.0** in week 48 compared with **223.7** in week 49.
- **Musculoskeletal :**Enhanced passive rate was **0.0** in week 48 compared with **272.5** in week 49. EHR data mining rate was **668.9** in week 48 compared with **447.4** in week 49.
- **Neurological :** Enhanced passive rate was **0.0** in week 48 compared with **0.0** in week 49. EHR data mining rate was **501.7** in week 48 compared with **223.7** in week 49.
- **Rash :** Enhanced passive rate was **0.0** in week 48 compared with **272.5** in week 49. EHR data mining rate was **0.0** in week 48 compared with **671.1** in week 49.
- **Respiratory/Miscellaneous :** Enhanced passive rate was **726.4** in week 48 compared with **272.5** in week 49. EHR data mining rate was **668.9** in week 48 compared with **1342.3** in week 49**.**
- **Sensitivity/anaphylaxis :** Enhanced passive rate was **0.0** in week 48 compared with **0.0** in week 49. EHR data mining rate was **0.0** in week 48 compared with **0.0** in week 49.

Comment:

The proportion of the practice population vaccinated continued to increase this week. The most common possible adverse event categories this week were respiratory/miscellaneous, and fever/pyrexia.

Influenza vaccine exposure rates

- **Cumulative vaccine exposure rates: All age groups, 2015 ***



* The vaccination exposure rates are a percentage of all registered patients in the pilot practices.

- **Cumulative vaccine exposure rates: All age groups, by vaccine brand, 2015 ***

	GSK vaccine	Non-GSK vaccine
<1yr		
1-4yrs	10.66	16.22
5-14yrs	3.99	18.31
15-24yrs	4.02	2.94
25-44yrs	5.48	5.58
45-64yrs	13.50	12.27
65-74yrs	59.32	48.23
75-84yrs	78.97	60.38
85+yrs	76.15	61.53
All ages	23.33	18.70

* The GSK vaccine rates are based on the vaccine exposure rates in 2 out of 9 of the pilot practices.

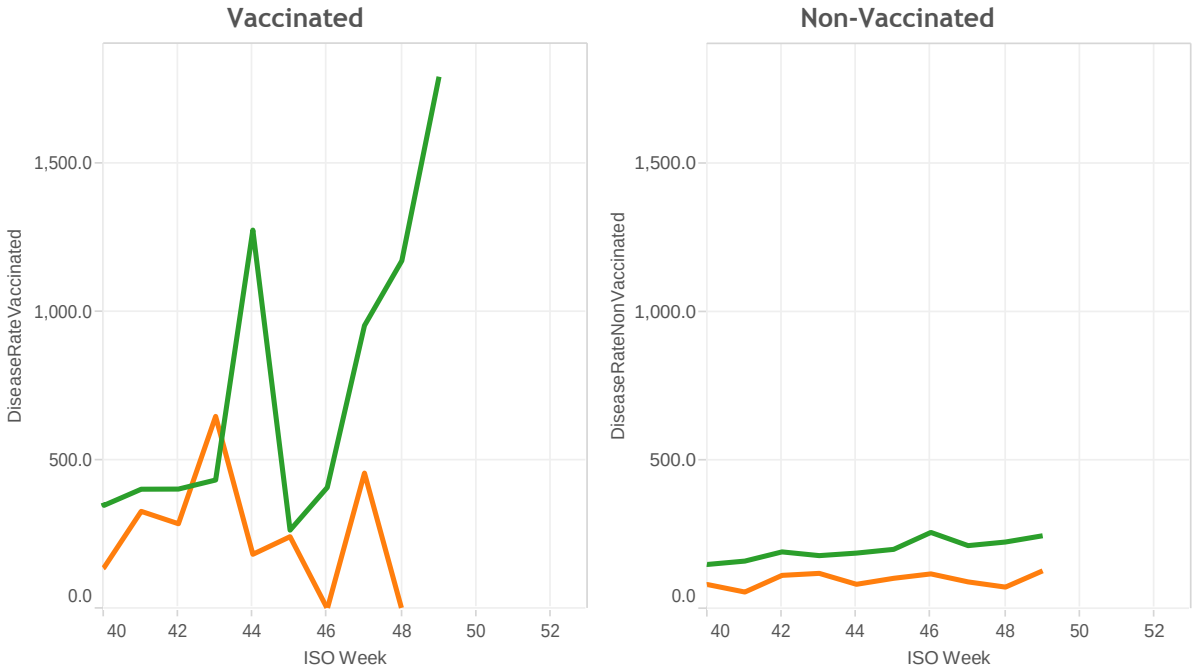
- **Key denominators**

	Registered Patients	Vaccinated Patients	Vaccination Rate
Non-GSK vaccine	65,215	12,194	18.70
GSK vaccine	15,420	3,597	23.33
Grand Total	80,635	15,791	19.58

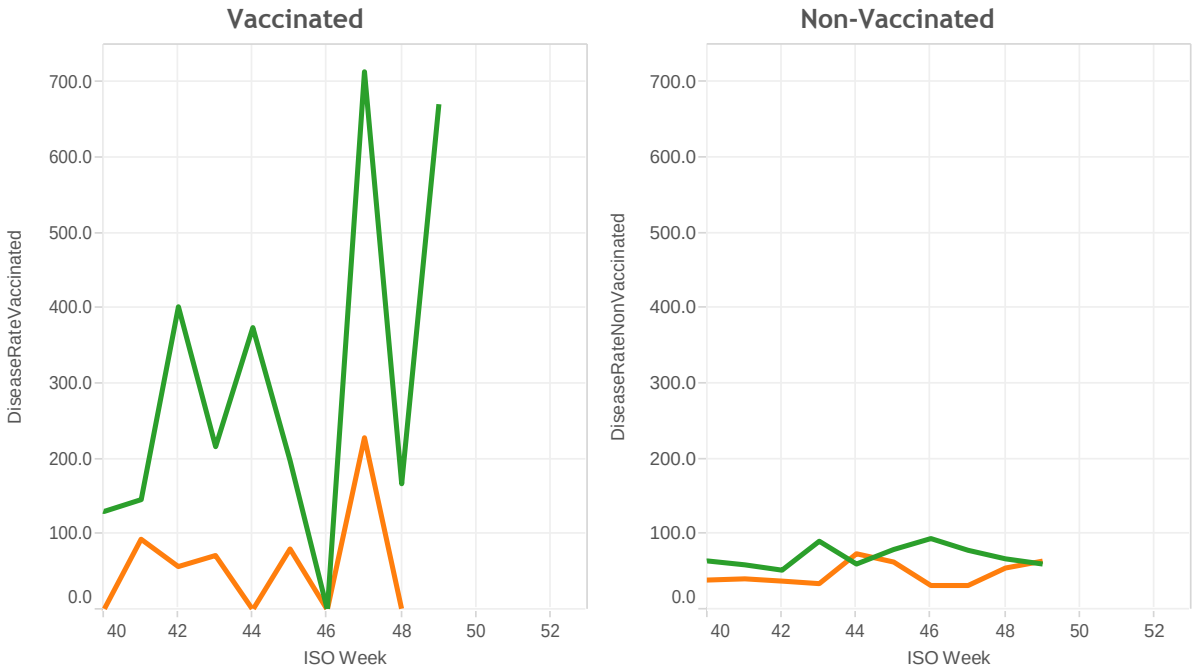
	Registered Patients	Vaccinated Patients	Vaccination Rate
EHR data mining	51,632	8,587	16.63
Enhanced passive	29,003	7,204	24.84
Grand Total	80,635	15,791	19.58

Possible adverse event rates by EMA surveillance condition

- **Fever/Pyrexia by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

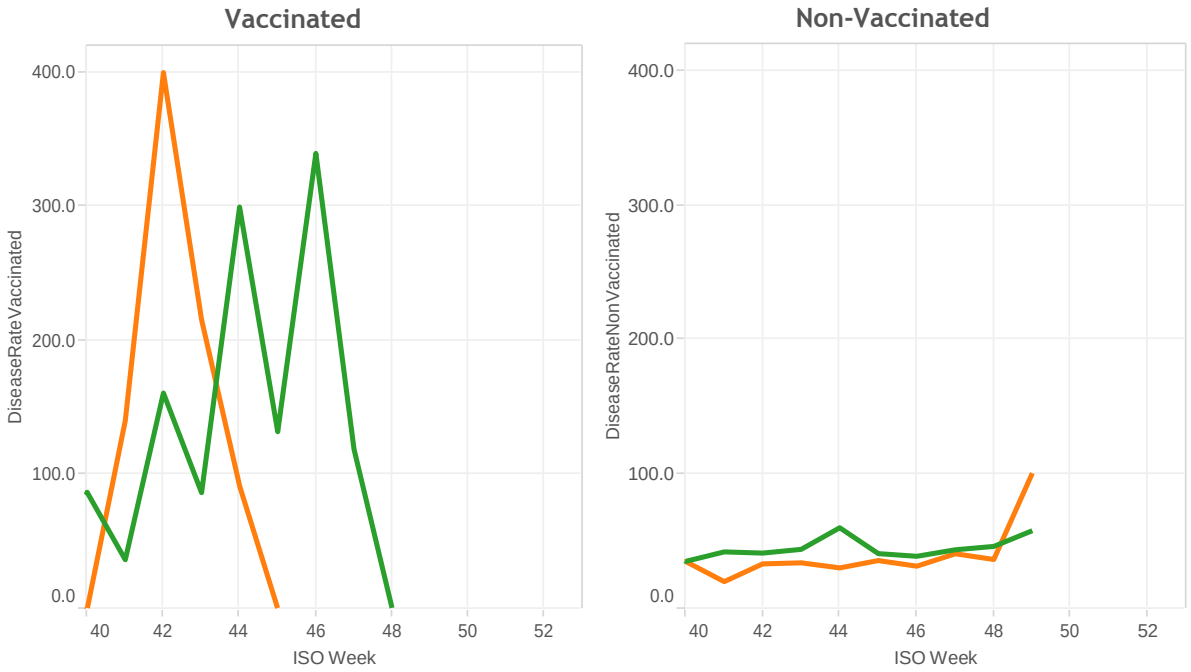


- **Gastrointestinal by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

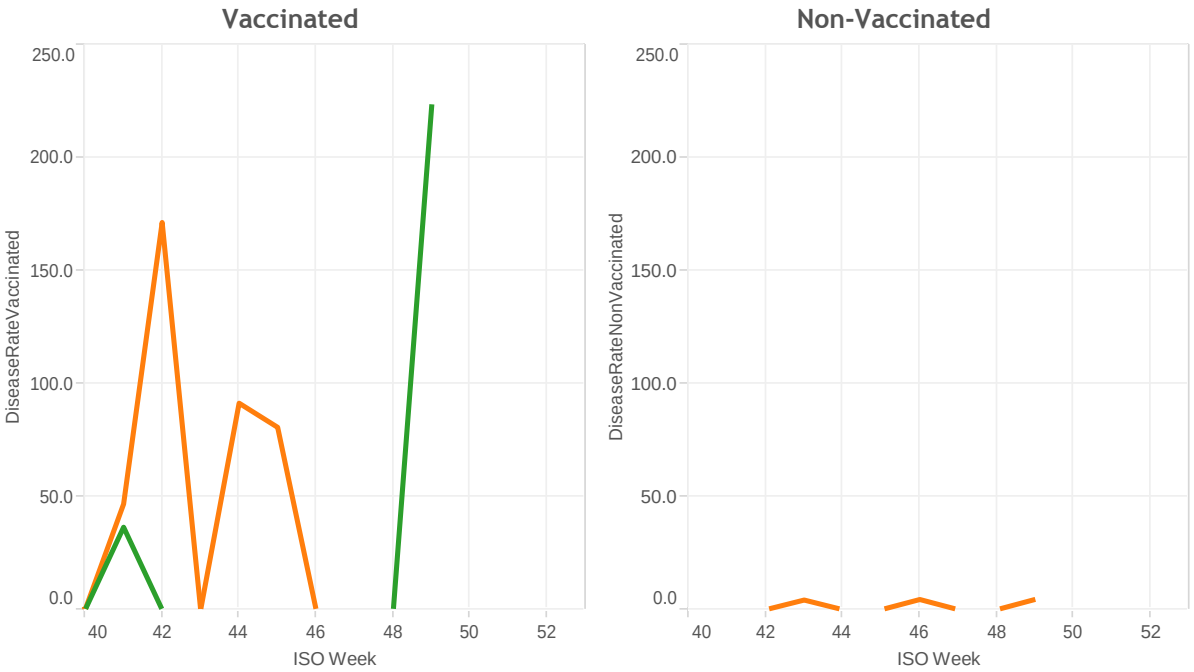


Possible adverse event rates by EMA surveillance condition

- **General non-specific symptoms by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

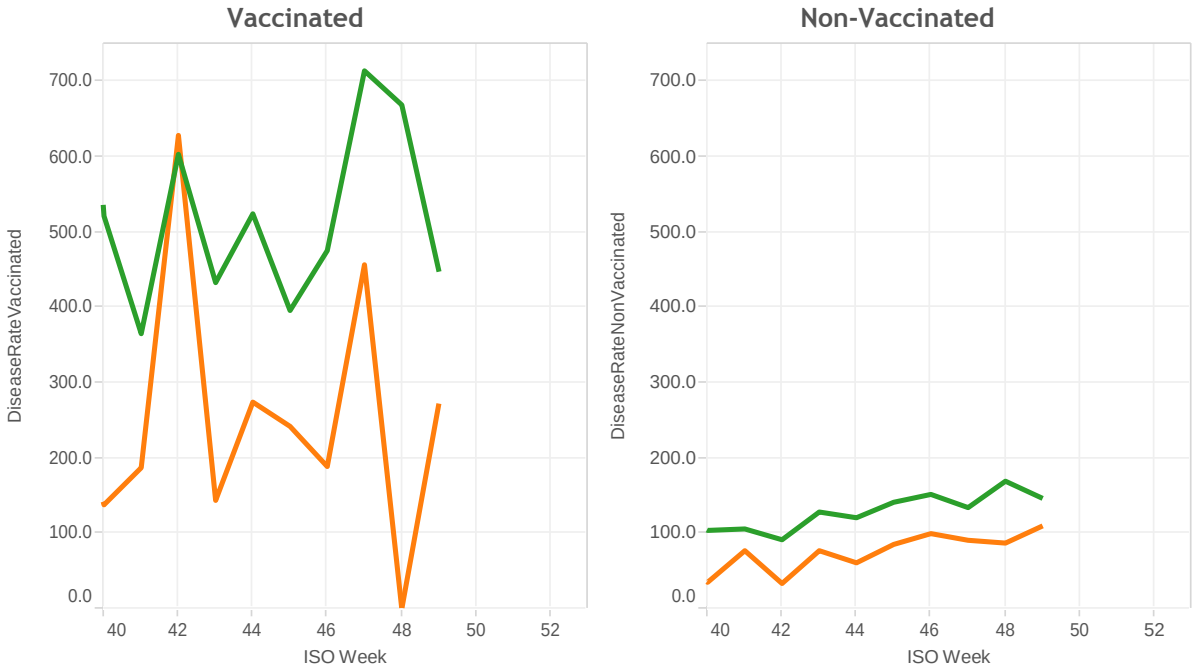


- **Local symptoms by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

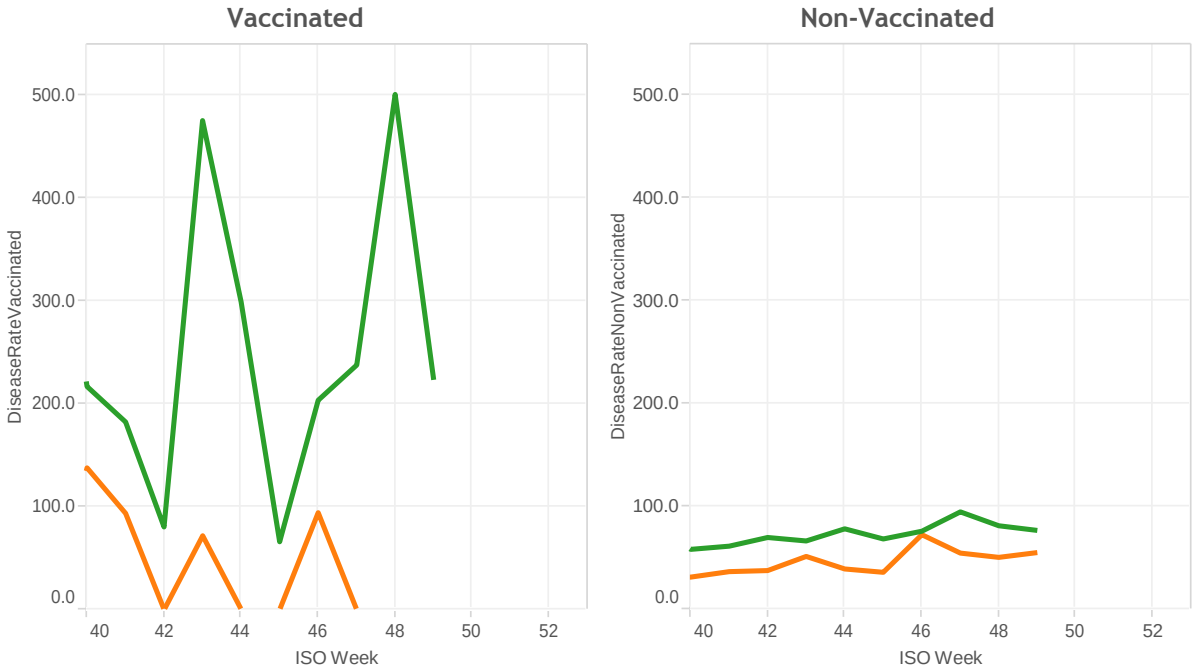


Possible adverse event rates by EMA surveillance condition

- **Musculoskeletal by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**

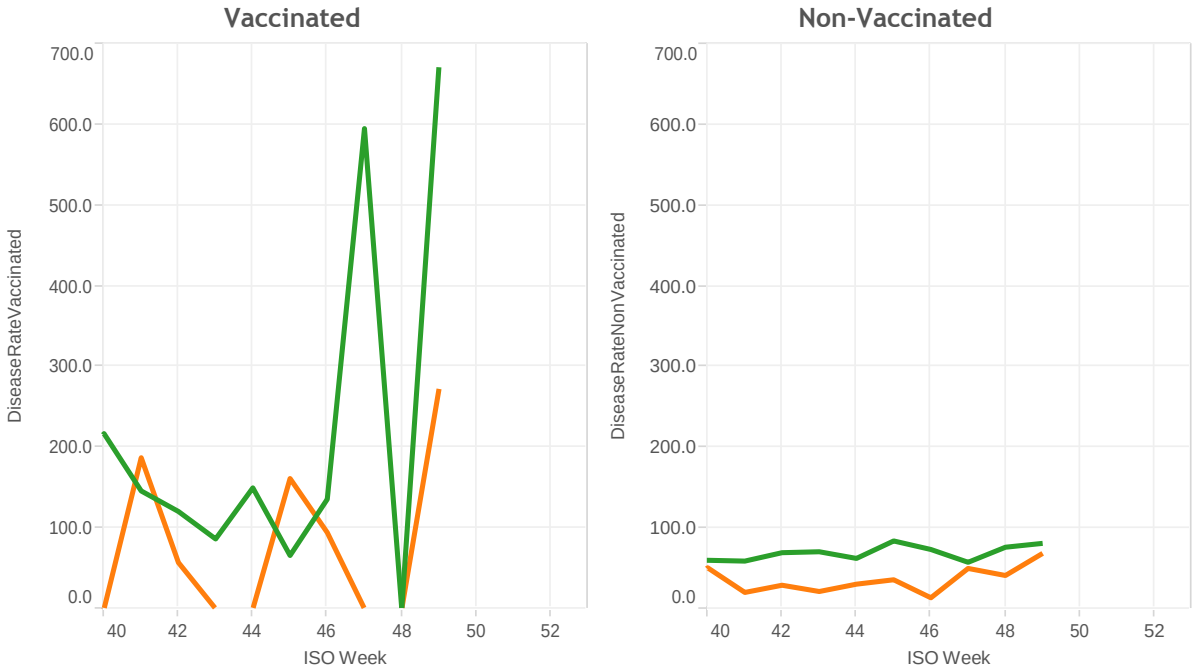


- **Neurological by Enhanced passive or EHR data mining: Incidence rates per 100,000, 2015**

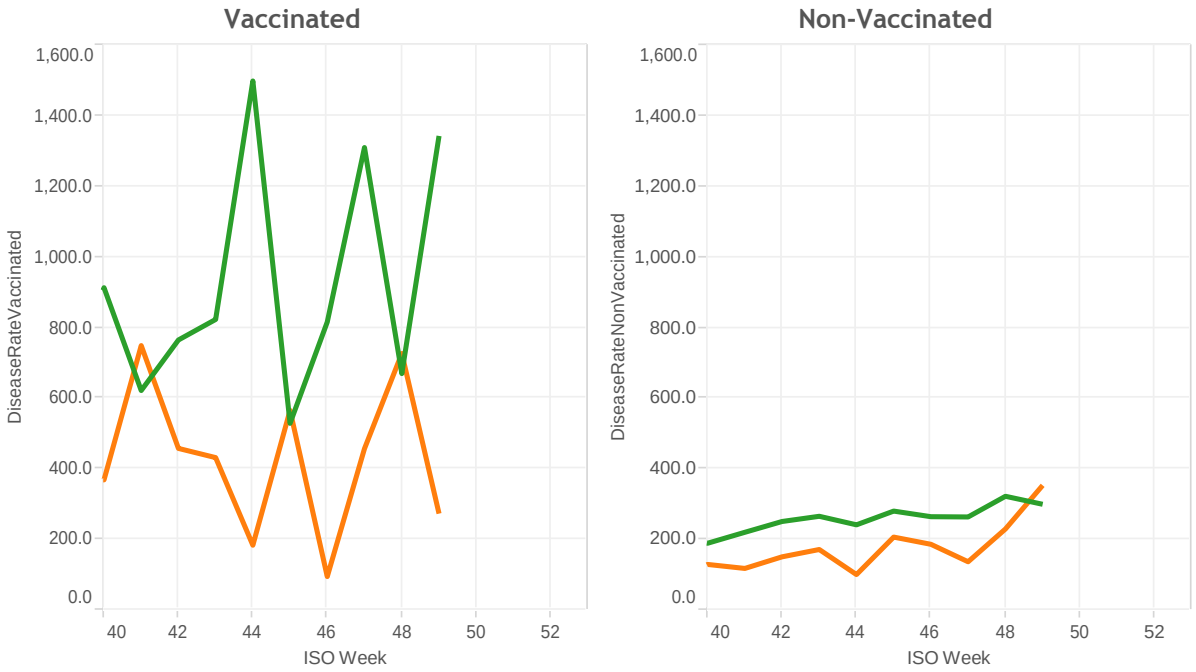


Possible adverse event rates by EMA surveillance condition

- **Rash by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**



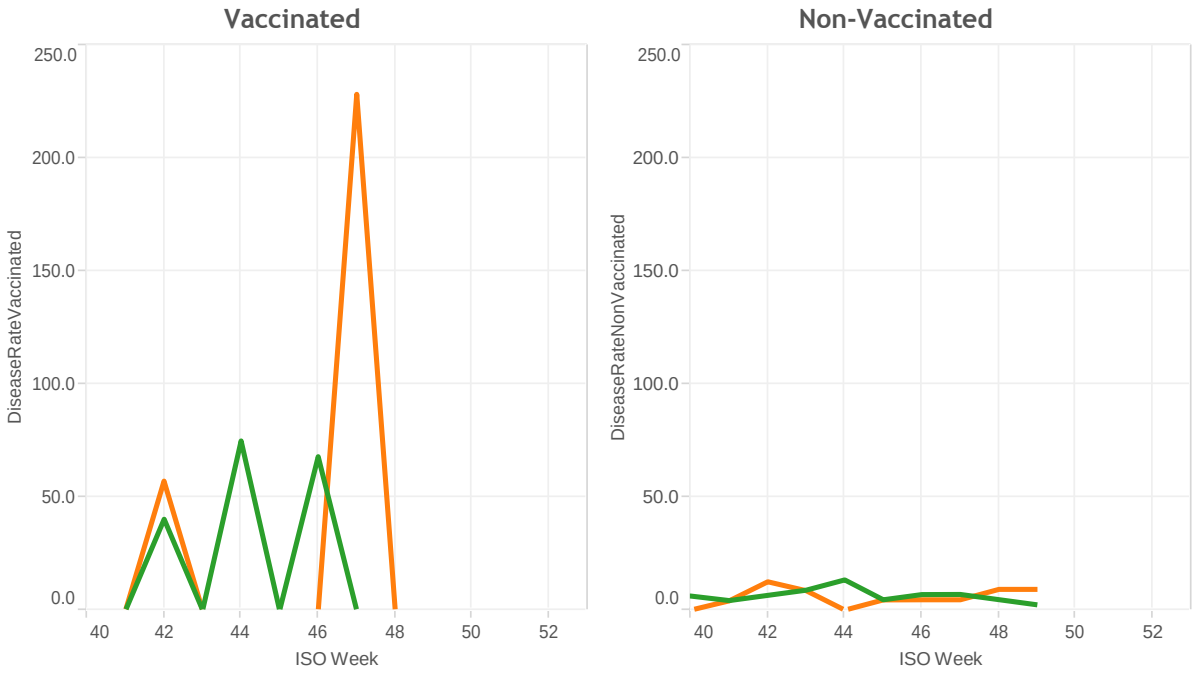
- **Respiratory/Miscellaneous by Enhanced passive or EHR data mining practices: Incidence rates per 100,000, 2015**



Possible adverse event rates by EMA surveillance condition, and weekly summary by vaccine brand

EHR data mining Enhanced passive

- **Sensitivity/Anaphylaxis by Enhanced passive or EHR data mining: Incidence rates per 100,000, 2015**



- **Possible adverse events by GSK or non-GSK vaccines: Incidence rates per 100,000, 2015 ****

Week number		49	48	47	46	45
Week beginning		30/11/2015	23/11/2015	16/11/2015	09/11/2015	02/11/2015
Week ending		06/12/2015	29/11/2015	22/11/2015	15/11/2015	08/11/2015
Fever/ ˈyrexia	GSK	0.0	0.0	621.1	0.0	511.1
	Non-GSK	1,199.4	829.4	836.8	303.3	184.6
Gastrointestinal	GSK	0.0	0.0	0.0	0.0	170.4
	Non-GSK	449.8	118.5	732.2	0.0	138.4
General symptoms	GSK	0.0	0.0	0.0	0.0	0.0
	Non-GSK	0.0	0.0	104.6	252.8	92.3
Local symptoms	GSK	0.0	0.0	0.0	0.0	170.4
	Non-GSK	149.9	0.0	0.0	0.0	0.0
Musculoskeletal	GSK	680.3	0.0	621.1	361.0	511.1
	Non-GSK	299.9	473.9	627.6	353.9	276.9
Neurological	GSK	0.0	0.0	0.0	180.5	0.0
	Non-GSK	149.9	355.5	209.2	151.7	46.1
Rash	GSK	680.3	0.0	0.0	180.5	340.7
	Non-GSK	449.8	0.0	523.0	101.1	46.1
Respiratory/Miscellaneous	GSK	680.3	1,796.4	621.1	180.5	511.1
	Non-GSK	899.6	473.9	1,150.6	606.7	553.8
Sensitivity/Anaphylaxis	GSK	0.0	0.0	0.0	0.0	0.0
	Non-GSK	0.0	0.0	104.6	50.6	0.0

0.0 200.0 400.0

** It must be noted that the two GSK practices are both conducting enhanced passive surveillance.

Weekly summary of possible adverse event rates by EMA surveillance condition and practice type

- **Possible adverse events by Enhanced passive or EHR data mining practices: Incidence rates per 100,000 and count of episodes, 2015**

Week number		49		48		47		46		45	
Week beginning		30/11/2015		23/11/2015		16/11/2015		09/11/2015		02/11/2015	
Week ending		06/12/2015		29/11/2015		22/11/2015		15/11/2015		08/11/2015	
		Episodes	Rate	Episodes	Rate	Episodes	Rate	Episodes	Rate	Episodes	Rate
Fever/Pyrexia	EHR data mining	8	1,789.7	7	1,170.6	8	952.4	6	407.6	4	264.0
	Enhanced passive	0	0.0	0	0.0	2	456.6	0	0.0	3	242.1
Gastrointestinal	EHR data mining	3	671.1	1	167.2	6	714.3	0	0.0	3	198.0
	Enhanced passive	0	0.0	0	0.0	1	228.3	0	0.0	1	80.7
General symptoms	EHR data mining	0	0.0	0	0.0	1	119.0	5	339.7	2	132.0
	Enhanced passive	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Local symptoms	EHR data mining	1	223.7	0	0.0	0	0.0	0	0.0	0	0.0
	Enhanced passive	0	0.0	0	0.0	0	0.0	0	0.0	1	80.7
Musculoskeletal	EHR data mining	2	447.4	4	668.9	6	714.3	7	475.5	6	396.0
	Enhanced passive	1	272.5	0	0.0	2	456.6	2	188.7	3	242.1
Neurological	EHR data mining	1	223.7	3	501.7	2	238.1	3	203.8	1	66.0
	Enhanced passive	0	0.0	0	0.0	0	0.0	1	94.3	0	0.0
Rash	EHR data mining	3	671.1	0	0.0	5	595.2	2	135.9	1	66.0
	Enhanced passive	1	272.5	0	0.0	0	0.0	1	94.3	2	161.4
Respiratory/ Miscellaneous	EHR data mining	6	1,342.3	4	668.9	11	1,309.5	12	815.2	8	528.1
	Enhanced passive	1	272.5	3	726.4	2	456.6	1	94.3	7	565.0
Sensitivity/ Anaphylaxis	EHR data mining	0	0.0	0	0.0	0	0.0	1	67.9	0	0.0
	Enhanced passive	0	0.0	0	0.0	1	228.3	0	0.0	0	0.0

Registered Patients	EHR data mining	51,632	51,485	51,366	51,236	51,151
	Enhanced passive	29,003	28,877	28,802	28,703	28,633
Vaccinated Patients	EHR data mining	8,587	8,366	8,118	7,748	7,262
	Enhanced passive	7,204	7,082	6,816	6,656	6,366
Registered Patients	**Total**	80,635	80,977	80,955	80,936	80,911
Vaccinated Patients	**Total**	15,791	15,448	14,934	14,404	13,628

Further information:

Post-authorisation safety surveillance pilot study

The European Medicines Agency (EMA) has set out new requirements for influenza vaccine safety surveillance that all Marketing Authorisation Holders (MAHs) providing vaccines in the EU must address. This pilot, funded by GlaxoSmithKline and conducted by the [redacted] demonstrates the potential of routinely collected data in the UK to provide timely and relevant information on influenza vaccine safety.

We are assessing adverse event of interest (AEI) frequencies among subjects who have received the influenza vaccine, using routinely collected data in nine primary care practices. AEIs up to 14 days from the date of vaccination are included for vaccinated patients. We are also providing the rate of these events in non-vaccinated patients, to assess background rates and trends. Where these conditions are found in non-vaccinated subjects we call them illness-disease episodes (IDE).

Three practices are taking part in the enhanced passive surveillance sub-study, where a reporting card has been given to vaccinated patients to return to the practices.

This report shows the weekly data flow capturing vaccine coverage, and proportions of patients reporting possible AEIs within the EMA's surveillance condition categories. The results of this pilot will be used to assess whether the data collected in the study meet the requirements of enhanced safety surveillance as stipulated in the interim guidance issued by EMA in April 2014.

This pilot study has received [redacted] approval (REF: 15/LO/1254).

How rates of possible adverse events are calculated

Denominator: The vaccinated denominator are all registered patients in the participating practices who have received the seasonal influenza vaccine in the preceding 2 weeks. The non-vaccinated denominator are all registered patients who have not received the seasonal influenza vaccine to date.

Numerator: The numerator for the vaccinated patients is the number of possible adverse events occurring during the current study week, which happened within a 14-day window after the patient received the seasonal influenza vaccine. The numerator for the non-vaccinated patients is the number of possible adverse events occurring during the study week, for non-vaccinated patients.

Detailed numerators and denominators for the vaccinated patients are stated in graph (L), page 8.

Vaccinated and non-vaccinated comparisons

This pilot study is not designed to provide a formal comparison of the two groups, but the rates of possible AEIs in the non-vaccinated population are included to provide a crude background rate. In future years, once more data has been collected, a more accurate background rate could be established using a 5 year average.

Timeliness of the data

In routine primary care data, the date of recording may differ from the date of the event. Sometimes GPs may add an entry to the patient's record several weeks after the date of the event. Usually, this lag in recording would not be greater than 6 weeks. Therefore, it is expected that each week there may be a small variation in the AEI rates from previous weeks, as new data is recorded.

Further information:

Data extraction process and information governance

Data are extracted twice weekly from practice systems by Apollo Medical Systems on behalf of the [redacted] Patients who have withheld consent for data sharing are excluded from the extraction process. Data are pseudonymised as close to source as possible.

Data are held on secure servers at the Section of Clinical Medicine and Ageing at the [redacted] Both Apollo and the [redacted] are registered and compliant with the Data Protection Act and fully compliant with all relevant HSCIC and NHS data information governance best practice.

For further information, please contact:

Professor [redacted]
[redacted]

[redacted]

Appendix B

Feedback on possible adverse events following vaccination

The European Medicines Agency (EMA), as part of the monitoring of the continuing safety of the influenza vaccination, has circulated a list of codes for possible adverse events that may be associated with vaccination.

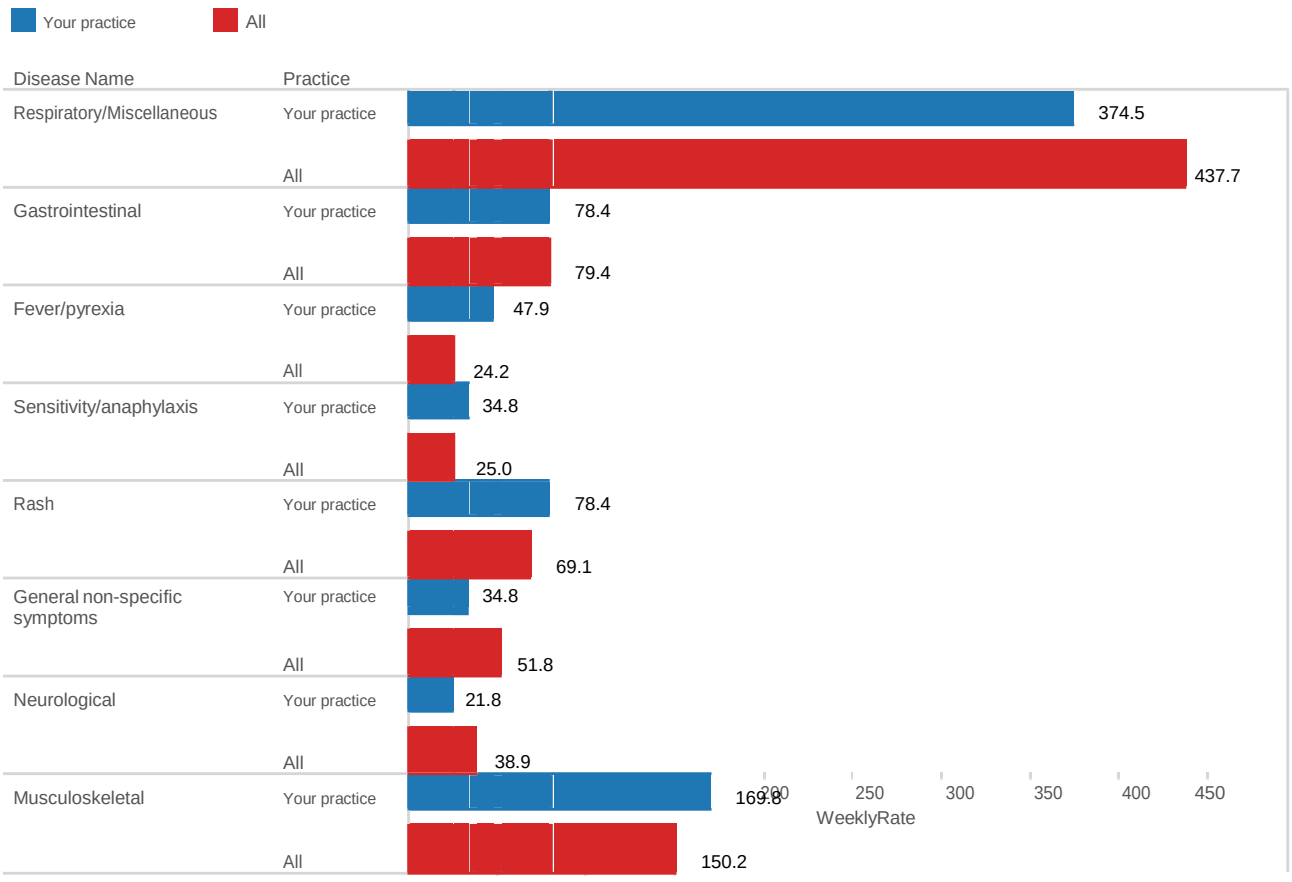
Data from will be used to monitor these possible adverse events, via twice-weekly data extract.

It is of course essential for this work that the data is accurate and that these codes are used consistently throughout the flu season. We therefore attach a table showing how many times the codes on the EMA list have been recorded in 's patient records in the 14 days from XXXX-XX-XX to XXXX-XX-XX.

Please continue to use these codes for all patients, whether or not they have been recently vaccinated. **Use of these codes does not imply a causal link between the adverse event and vaccination – any association will emerge from the data analysis.** This analysis will only be valid if the codes are used consistently for all relevant cases, regardless of the patient's vaccination status. It is therefore essential that these codes are used for all appropriate cases, whether or not the patient has been recently vaccinated.

Thank you very much for your help with this project – your input is crucial for ensuring that the influenza vaccination continues to be both safe and protective for patients

Following graph provides a visualization of compared with 7 other adverse events monitoring practices



The following table provides the total counts of possible adverse events for the 2015-09-04 to 2015-09-21 for your practice.

Disease Name	EMA surveillance condition	ReadCode Type	
Respiratory/Miscellaneous	Conjunctivitis	Preferred Read Code (F4C0.)	5
		Other Read Codes	0
	Rhinorrhoea	Preferred Read Code (1C83.)	0
		Other Read Codes	0
	Nasal congestion	Preferred Read Code (H1y1z)	0
		Other Read Codes	3
	Epistaxis	Preferred Read Code (R047.)	3
		Other Read Codes	22
	Coryza	Preferred Read Code (H00..)	1
		Other Read Codes	0
	Cough	Preferred Read Code (171..)	24
		Other Read Codes	1
	Oropharyngeal pain	Preferred Read Code (1922.)	1
		Other Read Codes	0
	Oropharyngeal pain	Preferred Read Code (1CB3.)	0
		Other Read Codes	0
	Hoarseness	Preferred Read Code (1CA2.)	1
		Other Read Codes	2
	Wheezing	Preferred Read Code (1737.)	3
		Other Read Codes	20
Gastrointestinal	Decreased appetite	Preferred Read Code (R0300)	0
		Other Read Codes	2
	Nausea	Preferred Read Code (198..)	3
		Other Read Codes	0
	Vomiting	Preferred Read Code (199..)	2
		Other Read Codes	0
	Diarrhoea	Preferred Read Code (19F..)	11
		Other Read Codes	0
Fever/pyrexia	Fever	Preferred Read Code (165..)	9
		Other Read Codes	0
	Mild fever (<38.5° C rectal) High fever (>39.5°C)	Preferred Read Code (2E3..)	2
		Other Read Codes	0
Sensitivity/anaphylaxis	Hypersensitivity reactions	Preferred Read Code (SN52.)	1
		Other Read Codes	0
	Anaphylactic reactions	Preferred Read Code (SN52.)	0
		Other Read Codes	0
	Facial oedema	Preferred Read Code (16J5.)	0
		Other Read Codes	7
	Local erythema	Preferred Read Code (SP3y5)	0
		Other Read Codes	0
Rash	Rash	Preferred Read Code (M130.)	0
		Other Read Codes	18
	Generalised rash	Preferred Read Code (2I14.)	0
		Other Read Codes	0
	Local erythema	Preferred Read Code (SP3y5)	0
		Other Read Codes	0
General non-specific symptoms	Irritability	Preferred Read Code (225A.)	0
		Other Read Codes	1
	Drowsiness	Preferred Read Code (1B67.)	0
		Other Read Codes	1
	Fatigue	Preferred Read Code (168..)	3
		Other Read Codes	0
	Malaise	Preferred Read Code (N037.)	0
		Other Read Codes	3

The following table provides the total counts of possible adverse events for the 2015-09-04 ***to*** 2015-09-21 ***for your practice.***
(Continues from previous page..)

Disease Name	EMA surveillance condition	ReadCode Type	
Neurological	Peripheral tremor	Preferred Read Code (1B22.)	0
		Other Read Codes	0
	Guillain-Barre Syndrome (GBS)	Preferred Read Code (F3700)	0
		Other Read Codes	0
	Seizure/ Febrile convulsions	Preferred Read Code (1B64.)	0
		Other Read Codes	0
	Seizure/ Febrile convulsions	Preferred Read Code (1B6B.)	0
		Other Read Codes	0
	Headache	Preferred Read Code (1B1G.)	5
		Other Read Codes	0
Musculoskeletal	Muscle aches/ myalgia	Preferred Read Code (N2410)	5
		Other Read Codes	34
	Arthropathy	Preferred Read Code (N037.)	0
		Other Read Codes	0

Possible adverse event code list for your reference

Disease Name	EMA surveillance Condition	Discription	Read Code
Respiratory/Miscellaneous	Conjunctivitis	Acute conjunctivitis	F4C0.
	Rhinorrhoea	Rhinorrhoea	1C83.
	Nasal congestion	Nasal airway obstruction	H1y1z
	Epistaxis	Epistaxis	R047.
	Coryza	Acute coryza	H00..
	Cough	Cough	171..
	Oropharyngeal pain	Sore mouth/Throat pain	1922.
	Oropharyngeal pain	Sore mouth/Throat pain	1CB3.
	Hoarseness	Hoarse	1CA2.
	Wheezing	Wheezing	1737.
Gastrointestinal	Decreased appetite	Loss of appetite	R0300
	Nausea	Nausea	198..
	Vomiting	Vomiting	199..
	Diarrhoea	Diarrhoea	19F..
Fever/pyrexia	Fever	Fever symptoms	165..
	Mild fever (<38.5° C rectal) High fever (>39.5°C)	O/E – Temperature level	2E3..
Sensitivity/anaphylaxis	Hypersensitivity reactions	Adverse drug reaction/Vaccine allergy	SN52.
	Anaphylactic reactions	Drug-induced anaphylaxis	SN501
	Facial oedema	Facial swelling	16J5.
	Local erythema	Erythema at injection site	SP3y5
Rash	Rash	Drug-induced rash	M130.
	Generalised rash	Rash	2I14.
	Local erythema	Erythema at injection site	SP3y5
General non-specific symptoms	Irritability	O/E - Irritable	225A.
	Drowsiness	Drowsiness	1B67.
	Fatigue	Fatigue	168..
Neurological	Peripheral tremor	Tremor	1B22.
	Guillain-Barre Syndrome (GBS)	Guillain-Barre Syndrome	F3700
	Seizure/ Febrile convulsions	Convulsion/Febrile convulsion	1B64.
	Seizure/ Febrile convulsions	Convulsion/Febrile convulsion	1B6B.
	Headache	Headache	1B1G.
Musculoskeletal	Muscle aches/ myalgia	Myalgia	N2410
	Arthropathy	Post-immunisation arthropathy	N037.

Appendix C

[redacted]

INFORMATION SHEET FOR GP PRACTICES – ACTIVE SURVEILLANCE

Project title: European Medicines Agency (EMA) post-authorisation safety study of influenza vaccine

Overview

We invite you to take part in a research study. Please take time to read the following information. The proposed study represents a pilot to explore the use of routinely collected data in England to provide timely and relevant information on influenza vaccine safety. The research is carried out by the [redacted] in collaboration with GlaxoSmithKline Biologicals.

Background and Rationale

The European Medicines Agency (EMA) has set out new requirements for influenza vaccine safety surveillance that all Marketing Authorisation Holders (MAHs) providing vaccines in the EU must address. The key objective of the EMA enhanced safety surveillance is to rapidly detect a significant increase in the frequency and/or severity of expected reactions (local, systemic or allergic reactions) that may indicate a potential or more serious risk, as exposure to the vaccine increases.

The objective of the study is to conduct a pilot assessing adverse event of interest (AEI) frequencies among flu-vaccinated subjects using routinely collected data in nine primary care practices. Our primary surveillance is of 7-day AEI, post vaccination, but we will not exclude events recorded outside this window, which will be analysed separately. Three of these nine practices will take part in the active surveillance sub-study.

What is the design of the study?

We have recruited nine practices representing urban and rural localities across England, and the three major computerised medical record (CMR) suppliers in the UK. The anticipated start date for data collection will be in September 2015.

The method and governance procedure has been developed by the [redacted] as part of previous work with the [redacted] and Public Health England (PHE), using an approved provider, Apollo Medical Software Solutions Ltd. Apollo extracts data using the Apollo automated extraction system. Communication is via a SOAP (Simple Object Access Protocol) web service, no special firewall configuration is needed. These arrangements may change

from time-to-time and we will notify members if any changes occur. For the active surveillance sub-study, patients will be given AEI reporting cards by practice staff to complete; the data from completed cards will be entered in the CMR by practice staff.

Data extractions will be conducted in accordance with the Research Group's standard operating procedures in data extraction, pseudonymisation, and transfer. All data are stored and managed by the [redacted] The information security policies and procedures of the Research Group have been approved by the NHS Health and Social Care Information Centre (HSCIC). Details of the departmental information governance policies and procedures can be found in:
http://www.clininf.eu/about/information-governance.html

Why have I been invited to take part?

The study is part of a research programme which aims to explore cases of adverse events of interest following flu immunisation. You have invited because your practice has expressed interest in becoming part of a research network within the [redacted] and because you meet representativeness criteria (geographic location and computerised medical record system) for this study.

What will happen if I take part?

You will be contacted by [redacted] and Apollo Medical Software Solutions Ltd to sign data extraction agreements. The GP practices will be supported by the [redacted] and the Research Team led by Prof [redacted] The responsibilities of the GP practices are outlined below.

What are my responsibilities?

If you agree to take part in the study, you will be required to provide such support as may be reasonably required to achieve its aims. Practices will be required to facilitate access for data extraction. In addition, as an active surveillance practice, staff will be required to distribute reporting cards to patients and to enter the data from these into the system.

What are the possible benefits of taking part?

The proposed study will help assess the feasibility of an influenza vaccine safety monitoring system using routine data collected in primary care, which will help patients receiving influenza vaccines.

Who can I contact for more information?

Prof [redacted]
[redacted]
e-mail: [redacted]
Telephone: [redacted]

Dr [redacted]
Project Manager
e-mail: [redacted]
Telephone: [redacted]

[redacted]

INFORMATION SHEET FOR GP PRACTICES – PASSIVE SURVEILLANCE

Project title: European Medicines Agency (EMA) post-authorisation safety study of influenza vaccine

Overview

We invite you to take part in a research study. Please take time to read the following information. The proposed study represents a pilot to explore the use of routinely collected data in England to provide timely and relevant information on influenza vaccine safety. The research is carried out by the [redacted] in collaboration with GlaxoSmithKline Biologicals.

Background and Rationale

The European Medicines Agency (EMA) has set out new requirements for influenza vaccine safety surveillance that all Marketing Authorisation Holders (MAHs) providing vaccines in the EU must address. The key objective of the EMA enhanced safety surveillance is to rapidly detect a significant increase in the frequency and/or severity of expected reactions (local, systemic or allergic reactions) that may indicate a potential or more serious risk, as exposure to the vaccine increases.

The objective of the study is to conduct a pilot assessing adverse event of interest (AEI) frequencies among flu-vaccinated subjects using routinely collected data in nine primary care practices. Our primary surveillance is of 7-day AEI, post vaccination, but we will not exclude events recorded outside this window, which will be analysed separately. Three of these nine practices will take part in the active surveillance sub-study.

What is the design of the study?

We have recruited nine practices representing urban and rural localities across England, and the three major computerised medical record (CMR) suppliers in the UK. The anticipated start date for data collection will be in September 2015.

The method and governance procedure has been developed by the [redacted] as part of previous work with the [redacted] and Public Health England (PHE), using an approved provider, Apollo Medical Software Solutions Ltd. Apollo extracts data using the Apollo automated extraction system. Communication is via a SOAP (Simple Object

Access Protocol) web service, no special firewall configuration is needed. These arrangements may change from time-to-time and we will notify members if any changes occur.

Data extractions will be conducted in accordance with the Research Group's standard operating procedures in data extraction, pseudonymisation, and transfer. All data are stored and managed by the [redacted] The information security policies and procedures of the Research Group have been approved by the NHS Health and Social Care Information Centre (HSCIC). Details of the departmental information governance policies and procedures can be found in:
http://www.clininf.eu/about/information-governance.html

Why have I been invited to take part?

The study is part of a research programme which aims to explore cases of adverse events of interest following flu immunisation. You have invited because your practice has expressed interest in becoming part of a research network within the [redacted] and because you meet representativeness criteria (geographic location and computerised medical record system) for this study.

What will happen if I take part?

You will be contacted by [redacted] and Apollo Medical Software Solutions Ltd to sign data extraction agreements. The GP practices will be supported by the [redacted] and the Research Team led by Prof [redacted] The responsibilities of the GP practices are outlined below.

What are my responsibilities?

If you agree to take part in the study, you will be required to provide such support as may be reasonably required to achieve its aims. Practices will be required to facilitate access for data extraction.

What are the possible benefits of taking part?

The proposed study will help assess the feasibility of an influenza vaccine safety monitoring system using routine data collected in primary care, which will help patients receiving influenza vaccines.

Who can I contact for more information?

Prof [redacted]
[redacted]
e-mail: [redacted]
Telephone: [redacted]

Dr [redacted]
Project Manager
e-mail: [redacted]
Telephone: [redacted]

[redacted]

INFORMATION SHEET FOR PATIENTS – ACTIVE SURVEILLANCE

Project title: European Medicines Agency (EMA) post-authorisation safety study of influenza vaccine

Overview

We invite you to take part in a research study. Please take time to read the following information. The proposed study will be exploring the use of General Practitioner (GP) data in providing up-to-date information about vaccine safety. The research is carried out by the [redacted] in collaboration with GlaxoSmithKline Biologicals.

Background and Rationale

The European Medicines Agency (EMA) has set out new requirements for influenza vaccine safety surveillance. The key objective of these requirements is to quickly detect a significant increase in the frequency and/or severity of reactions to vaccines (which could include rashes, headaches, or more severe allergic reactions) that may indicate a potential or more serious risk. The objective of this study is to explore using GP data in assessing the frequency and severity of influenza vaccine reactions (also known as adverse events of interest, or AEIs). We will assess AEIs happening up to 14 days after vaccination.

What is the design of the study?

We have recruited nine practices representing urban and rural localities across England. The method and governance procedure has been developed by the [redacted] as part of previous work with the [redacted] and Public Health England (PHE), using an approved provider, Apollo Medical Software Solutions Ltd.

In order to identify AEIs, this study will pull out routinely collected data held in the surgery for all patients who have been recently vaccinated with the influenza vaccine. Patient identifiable information (name & date of birth) will be converted in your surgery to an anonymous and encrypted format. No patient identifiable information will actually leave the surgery. In addition, patients who have received the vaccine will be asked to complete a reporting card with details of any AEIs.

What will happen if I take part?

After you receive your influenza vaccine, you will be asked by practice staff to complete a reporting card, which will need to be returned to the practice within 7-14 days after vaccination. This will be a Yellow Card, which is the standard reporting card used by the Medicines and Healthcare Products Regulatory Agency in

the UK. Practice staff will then record this information into your electronic record. We will then extract this data in an anonymised format. The information provided by the surgery is treated in the strictest confidence, and it is not possible to relate any results to you personally.

What are the possible benefits of taking part?

The proposed study will help assess a possible safety monitoring system for influenza vaccine safety, which will contribute to the safety of patients receiving influenza vaccines.

If you would like to find out more about this study or if you wish to opt out of this study, please talk to your GP or a receptionist. Alternatively, you could contact the research team directly:

Prof [redacted]
[redacted]
e-mail: [redacted]
Telephone: [redacted]

Dr [redacted]
Project Manager
e-mail: [redacted]
Telephone: [redacted]

ARE YOU HAVING A FLU VACCINE?

[redacted]

PATIENT INFORMATION: RESEARCH PROJECT IN THIS SURGERY

It is important to maintain a strong process to monitor vaccine safety, particularly for frequent vaccines such as the influenza vaccine. This surgery is taking part in a research programme to explore how influenza vaccine safety could be monitored using primary care data. This study is funded by GlaxoSmithKline Biologicals, and is conducted by the [redacted]

The main objective is to conduct a pilot **assessing adverse event of interest** (AEI) frequencies **among flu-vaccinated subjects** using routinely collected data in England to provide timely and relevant information on influenza vaccine safety. AEIs are reactions to vaccines, which could include rashes, headaches, or more severe allergic reactions.

How will it be carried out?

In order to identify AEIs, this study will pull out routinely collected data held in the surgery for all patients who have been recently vaccinated with the influenza vaccine. **Patient identifiable information (name & date of birth) will be converted in your surgery to an anonymous and encrypted format. No patient identifiable information will actually leave the surgery.** In addition, patients who have received the vaccine will be asked to complete a reporting card with details of any AEIs.

How will it affect me?

Patients who have received the vaccine will be asked to complete a reporting card, which will need to be returned to the practice within 7-14 days after vaccination. No additional treatment or assessments will be needed. **The information provided by the surgery is treated in the strictest confidence, and it is not possible to relate any results to you personally.**

Who has reviewed this information?

This study has been reviewed and approved for conduct by the National Research Ethics Committee. This committee reviews research studies to protect the rights and well being of the patients taking part.

If you would like to find out more about this study or if you wish to opt out of this study, please talk to your GP or a receptionist. Alternatively, you could contact the research team directly:

Prof [redacted]

[redacted]

Phone: [redacted]

E-mail: [redacted]

Dr [redacted]

Project Manager

Phone: [redacted]

E-mail: [redacted]

ARE YOU HAVING A FLU VACCINE?

PATIENT INFORMATION: RESEARCH PROJECT IN THIS SURGERY

It is important to maintain a strong process to monitor vaccine safety, particularly for frequent vaccines such as the influenza vaccine. This surgery is taking part in a research programme to explore how influenza vaccine safety could be monitored using primary care data. This study is funded by GlaxoSmithKline Biologicals, and is conducted by the [redacted]

The main objective is to conduct a pilot **assessing adverse event of interest** (AEI) frequencies **among flu-vaccinated subjects** using routinely collected data in England to provide timely and relevant information on influenza vaccine safety. AEIs are reactions to vaccines, which could include rashes, headaches, or more severe allergic reactions.

How will it be carried out?

In order to identify AEIs, this study will pull out routinely collected data held in the surgery for all patients who have been recently vaccinated with the influenza vaccine. **Patient identifiable information (name & date of birth) will be converted in your surgery to an anonymous and encrypted format. No patient identifiable information will actually leave the surgery.**

How will it affect me?

This project does not affect patients directly. No additional treatment or assessments will be needed. **The information provided by the surgery is treated in the strictest confidence, and it is not possible to relate any results to you personally.**

Who has reviewed this information?

This study has been reviewed and approved for conduct by the National Research Ethics Committee. This committee reviews research studies to protect the rights and wellbeing of the patients taking part.

If you would like to find out more about this study or if you wish to opt out of this study, please talk to your GP or a receptionist. Alternatively, you could contact the research team directly:

Prof [redacted]

[redacted]

Phone: [redacted]

E-mail: [redacted]

Dr [redacted]

Project Manager

Phone: [redacted]

E-mail: [redacted]

Appendix D

Tear along the dotted line

Confidential

Yellow Card

Use blue or black ink. Complete all the lines marked with ✳ and give as much other information as you can

1 About the suspected side effect

✳ **What were the symptoms of the suspected side effect, and how did it happen?** If there isn't enough space here, attach an extra sheet of paper.

How bad was the suspected side effect? Tick the box that best describes how bad the symptoms were.

✳ ☐ Mild ☐ Unpleasant, but did not affect everyday activities ☐ Bad enough to affect everyday activities ☐ Bad enough to see doctor
☐ Bad enough to be admitted to hospital ☐ Caused very serious illness ☐ Caused death ☐ Other

When did the side effect start?

How is the person feeling now? Tick the box that best describes whether the person still has symptoms of the suspected side effect.

✳ ☐ Better (no more symptoms) ☐ Getting better ☐ Still has symptoms ☐ More seriously ill ☐ Died ☐ Other

Can you give any more details? For example, did the person take or receive any other treatment for the symptoms? Did they stop taking the medicine as a result of the side effect?

2 About the person who had the suspected side effect

Who had the suspected side effect?

✳ ☐ You ☐ Your child ☐ Someone else

Information about the person Supply as much information as you can, even if you prefer not to give a name.

First name or initials Family name ☐ Male ☐ Female

✳ Age Weight ☐ kg ☐ stones/pounds Height ☐ metres ☐ feet/inches

Any other relevant information? For example, does the person have any medical conditions or allergies?

3 About the medicine(s) which might have caused the side effect

Give details of the medicine you suspect of causing the side effect.

Name of the medicine ☐ prescription ☐ bought in pharmacy ☐ bought elsewhere ☐ bought on the internet

Dosage (for example, one 250 mg tablet, twice a day)

What was it taken for?

Start date: End date: Did you stop because of side effects? ☐ Yes ☐ No

If you (or the person you're reporting for) were taking any other medicine at the same time (which might have caused an interaction), give details of it. If you need to give details of more than one other medicine, attach an extra sheet of paper.

Name of other medicine ☐ prescription ☐ bought in pharmacy ☐ bought elsewhere ☐ bought on the internet

Dosage (for example, one 250 mg tablet, twice a day)

What was it taken for?

Do you think this medicine might also have caused the side effect? ☐ Yes ☐ No ☐ Possibly

Start date: End date: Did you stop because of side effects? ☐ Yes ☐ No

Have you taken any other medicines or herbal remedies (as well as the above) **within the last 3 months?** ☐ Yes ☐ N

4 About your doctor *(optional)*

Would you like a copy of this report to be sent to your doctor?

☐ Yes ☐ No If Yes, give the doctor's name and address.

If you want us to send a copy of this report to any other healthcare professional, attach a separate sheet with their contact details.

If we need more medical information (such as test results), do we have your permission to contact your doctor directly for it?

☐ Yes ☐ No

Doctor's name

Address

Postcode

5 About you — the person making the report

We need contact details — please supply a full postal address, even if you prefer not to give a phone number or email address.

Title First name or initials Family name

Address

Postcode

Telephone number Email address

Please sign and date this form

I agree that the Medicines and Healthcare products Regulatory Agency (MHRA) can contact me to discuss the suspected side effect, and to ask for more information that might help understanding of the case.

Signed Date

CONFIDENTIAL

Protocol final

Protocol title: European Medicines Agency (EMA) post-authorisation safety study of influenza vaccine

Date of Protocol: Final version 2: 15 June 2015

[redacted] **team:**

[redacted][1]

[redacted]

[redacted][1]

[redacted]

[redacted][1]

[redacted]

[redacted][1]

[redacted]

GSK Team:

[redacted][2]
Director, Epidemiology
GSK Vaccines/Global HQ
[redacted]

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[2] GSK Vaccines
Rue de l'Institut 89
1330 Rixensart
Belgium

*Author for Correspondence

Table of contents

1. LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AEI	Adverse events of interest
CMR	Computerised Medical Record (system)
[redacted]	[redacted]
EMA	European Medicines Agency
GP	General Practitioner – A family physician providing NHS care to a registered list of patients
GPSoC	GP System of Choice, range of NHS approved computerised medical record systems that provide the required level of functionality to support primary care delivery
GSK	GlaxoSmithKline Biologicals
HSCIC	Health and Social Care information Centre (source of National data against which denominators and other population data can be checked)
HSCIC ODS	HSCIC Organisation Data Service – system that provides codes for all NHS bodies, including general practices and population data about these bodies
IGT	Information Governance Toolkit – standard set for holding health data
MAH	Marketing Authorisation Holders
NRES	National Research Ethics Service
NHS	National Health Service
PASS	Post Authorisation Safety study
PHE	Public Health England
QOF	Quality and Outcomes Framework
[redacted]	[redacted]
[redacted]	[redacted]
REC	Research Ethics Committee
RES	Research and Enterprise Support
SLA	Service level agreement
[redacted]	[redacted]

2. RESPONSIBLE PARTIES

United Kingdom

GSK Vaccines
Rue de l'Institut 89
1330 Rixensart
Belgium

3. ABSTRACT

Background:
The European Medicines Agency (EMA) has set out new requirements for influenza vaccine safety surveillance that all Marketing Authorisation Holders (MAHs) providing vaccines in the EU must address. The proposed study represents a pilot to explore the use of routinely collected data in the UK to provide timely and relevant information on influenza vaccine safety. UK primary care is highly computerised, though the major suppliers have different data models, coding systems, and methods of data access. Thus, a database approach may not be sufficient to meet the EMA commitment. As such, a sub-study will explore the utility of active solicitation of safety data from vaccinated subjects.

Objective:
To conduct a pilot assessing adverse event of interest (AEI) frequencies among flu-vaccinated subjects using routinely collected data in nine primary care practices. Our primary surveillance is of 7-day AEI, but we will not exclude events recorded outside this window, which will be analysed separately. Three practices will take part in the active surveillance sub-study.

Methods:
We will recruit nine practices representing urban and rural localities across England, and the three major computerised medical record (CMR) suppliers in the UK.

We will extract weekly data, using a method [redacted] developed for use in the national surveillance system, to allow passive observation of data; refreshed weekly from participating practices. We will evaluate 7-day AEI frequencies from this data. In three of these nine practices, we will also utilize a more active data collection approach.

This protocol will be submitted to the [redacted] for guidance on the necessary approvals for this surveillance, the consent required from patients and their carers, and the access to and use of data for this surveillance.

Expected outcomes:

- Weekly data flow that captures
    - Vaccination coverage by age strata and brand
    - Proportions of patients reporting pre-specified AEIs by age strata and brand
    - An assessment of data completeness and timeliness

This is a pilot study, the results of which will be used to assess the whether the data collected in the study meet the requirements of enhanced safety surveillance as stipulated in the interim guidance issued by EMA in April 2014.

4. PROJECT MILESTONES

Activity	2015											
	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Protocol writing												
Contract writing												
Ethical process												
Information privacy process												
Practice recruitment												
Data extraction												
Reporting												

Milestones

Milestone 1
Protocol is completed.
March 2015

Milestone 2
Contract to deliver pilot study is signed.
April2015

Milestone 3
Ethics and information privacy processes are approved.
June 2015

Milestone 4
Practice recruitment is finalised.
September 2015

Milestone 5
Weekly data extraction begins.
September 2015

Milestone 6
Weekly reports are sent to GSK.
November 2015

5. RATIONALE AND BACKGROUND

The European Medicines Agency (EMA) is a decentralised agency of the European Union (EU), located in London. The Agency is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the EU. Part of this responsibility is to coordinate the EU's safety-monitoring or pharmacovigilance system for medicines, monitor the safety of medicines through the EU network, and take action, if information indicates that the benefit-risk balance of a medicine has changed since it was authorised.

In response to a recent expansion of national vaccination programmes in EU member states, the European Medicines Agency has released interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU.[i] This set out new standards for surveillance. The key objective of the EMA enhanced safety surveillance is to rapidly detect a significant increase in the frequency and/or severity of expected reactions (local, systemic or allergic reactions) that may indicate a potential or more serious risk, as exposure to the vaccine increases. The interim EMA guidance provides suggested surveillance methods, but formal communications between Marketing Authorisation Holders (MAHs) and the EMA indicate that there is flexibility around the specifications due to heterogeneity in vaccine coverage, brand distribution, and data collection options across member states.

The present proposed collaborative study between MAH GlaxoSmithKline Biologicals (GSK) and the [redacted] is a pilot study which reflects the recommendations of EMA for enhanced safety surveillance. The present study will be conducted by the [redacted] at the [redacted] The primary purpose of the proposed pilot is to explore the potential of routine data to report what is required by EMA and what additional direct data may need to be collected. The results will inform decisions regarding future influenza vaccine safety surveillance activities in the UK.

The [redacted] in the [redacted] at [redacted] is the data and analysis hub for the [redacted] through a formal data sharing agreement. This work mainly comprises surveillance sponsored by Public Health England (PHE); the data processing, analysis capability, and leadership of the [redacted] is based at [redacted] The [redacted] is the gold standard sentinel network.[ii] The [redacted] network of practices has a membership designed to give national coverage of 1.5% of the population. The [redacted] team have updated and modernised its information processes.

The most important work of the network is its influenza surveillance; many practices have been involved in this work for decades. Data are uploaded from the network weekly, to a secure sever with the option to switch to twice weekly uploads at time of epidemics. The methods developed by

the [redacted] throughout its partnership with the [redacted] in influenza surveillance will be applied to this in-depth surveillance, with a focus on vaccine safety.

Seasonal influenza vaccines present several specific challenges for pharmacovigilance. These include immunisation in large population cohorts in a relatively short and fixed time period each year, and multiplicity of vaccine products on the market with the need for product-specific surveillance. There are also examples of batch-specific changes in manufacturing specifications during the product life-cycle, leading to unexpected new and emerging reactogenicity or other adverse immune response.

Pharmacovigilance systems for influenza vaccines need capability to rapidly detect and evaluate potential new safety concerns each influenza season. The aim is to mitigate risks before the peak period of seasonal immunisation. The main objective of enhanced safety surveillance is to detect and evaluate a potential increase in product and batch-specific reactogenicity and allergic events in near real-time in the earliest vaccinated cohorts. Enhanced surveillance must also be practicable in realistic clinical settings and administratively feasible every year.

The EMA Interim Guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU suggested that there are three options envisaged for enhanced surveillance:

- *Active surveillance:* Active follow-up of a cohort of children and adults for 7 days after immunisation for reactogenicity endpoints/adverse events.
- *Passive surveillance:* Rapidly estimate vaccine usage and facilitate passive adverse drug reaction (ADR) reporting, in order to derive reporting rate as a surrogate of incidence of the adverse events of interest (AEIs).
- *Data mining* or other use of electronic health record data.

In the UK, in response to the Chief Medical Office's letter published 25 May 2011[iii], the Department of Health recommended that seasonal influenza vaccine should be offered to the following eligible groups of GP patients including:

- All aged 65 years and over.
- All aged six months to 65 years falling in a clinical at-risk group (i.e. chronic respiratory disease, chronic heart disease, chronic kidney disease, chronic liver disease, chronic neurological disease, diabetes, and immunosuppression).
- People who are in receipt of a carer's allowance, or those who are the main carer of an elderly or disabled person whose welfare may be at risk if the carer falls ill.
- All pregnant women.

Expansion of national vaccination has created a greater need for timely information and reassurance on the balance of risks and benefits for those receiving the vaccines. This collaborative study is conceived in response to the EMA's call for enhanced safety surveillance.

This study will not only formulate a framework for enhanced safety surveillance in the UK, but will also contribute to an EU-wider programme of enhanced safety surveillance for seasonal influenza vaccines.

6. OBJECTIVES AND ENDPOINTS

The proposed in-depth surveillance aims to report vaccine coverage and AEIs from routine data extracted using methods that [redacted] now deploys to extract [redacted] surveillance data. Clinical data routinely collected as part of clinical consultations in primary care will be extracted from nine GP practices in order to estimate medically attended AEIs. The proposed study will also actively follow a cohort of patients who were exposed to seasonal influenza vaccination for 7 days in three of the nine GP practices using a customised card-based adverse drug reaction (ADR) or alternative data collection system. We will also provide data for use in determining whether or not these approaches are fit for enhanced surveillance of seasonal influenza vaccination by evaluating basic parameters of data completeness and timeliness.

Primary objectives:

- Weekly estimation of vaccine coverage, by age strata, CMO recommendation category, and brand
- Weekly reporting of AEI rates among subjects vaccinated against seasonal influenza, by age strata, co-morbidity and brand, from nine GP practices using CMR data
- Weekly reporting of AEI rates among subjects vaccinated against seasonal influenza, by age strata, co-morbidity and brand, from three GP practices using an active card-based ADR system

Secondary objectives:

- To assess the completeness of vaccination data in the CMR
- To assess the timeliness of vaccination data in the CMR
- To assess the completeness of AEI reporting in the CMR and through ADR card reporting
- To assess the timeliness of AEI reporting in the CMR and through ADR card reporting
- To assess whether the rates of the most frequently reported events are compatible with expectations from published rates in a comparable population

Primary endpoints:

- Patient counts and proportions of total registered patients vaccinated by age strata and co-morbidity, reported weekly and cumulatively by brand (also indicating those for whom brand data are unavailable)
- Patient counts and proportions of vaccinated patients with reported endpoints of interest by age strata and co-morbidity, reported weekly and cumulatively by brand (also indicating those for whom brand data are unavailable)

- Presentation with fever or other febrile illness
- Presentation related to local reaction
- Presentation related to general reaction (fatigue, myalgia, etc.)
- All other presentations that could plausibly be related to vaccination

Secondary endpoints:

- Proportion of those vaccinated for whom brand data and administration date are available in the CMR
- Mean (and standard deviation), median (and range) of the duration between vaccine administration and vaccination recording in the CMR
- Proportion of subjects, by age strata, given an ADR reporting card who return the completed card during the course of the study
- Proportion of subjects, by age strata, given an ADR reporting card who return the completed card within 14 days of vaccination
- Mean (and standard deviation), median (and range) of the time interval between vaccine administration and AEI reporting in the CMR and using the ADR card-based approach
- Mean (and standard deviation), median (and range) of the time interval between AEI reporting and recording in the CMR
- Incidence rates for the five most frequently reported AEs (where at least 5 cases are reported) reported alongside those available in the literature from a similar population (vaccinated or general population if vaccinated not available) within the same risk period and stratified by age when relevant and possible

7. RESEARCH METHODS

7.1.Study Design

Study setting and population

This pilot project will extract routinely collected primary care data from nine GP practices and an active surveillance approach in 3 of the 9 GP practices to estimate proportions of AEIs among influenza-vaccinated individuals.

The proposed pilot project will actively follow up a cohort of patients in three of the nine GP practices who were exposed to seasonal influenza vaccination in the months between 01/09/2015 and 30/11/2015, by using an existing card-based ADR reporting system, developed by the UK Medicines and Healthcare products Regulation Agency (MHRA). However, this will be customised to have fields that can be readily coded into the GP computerised medical record (CMR) system; and meet the requirements of the EMA. Patients will be issued with the appropriate ADR reporting card and invited to return the card to the GP surgeries after 7 days, but not later than 14 days post-vaccination.

We will look for practices ideally distributed across England (in London, a Northern city, and rural settings in the North and South) and aim to sample purposefully across these locations investigating the different brands of GP CMR systems. It is particularly important, in the first stages, to recruit large practices. We will rank practices based on our assessment of their potential compliance with the protocol requirements. Practices will be reimbursed for their involvement in this study, according to the National Institute of Health Research (NIHR) guidelines.

The average practice size in England and Wales is 7,034[iv], we estimate that data will be collected on a population of approximately 63,300 patients (across nine practices). In the period from September to December 2014, the seasonal influenza vaccine uptake for over 65 year olds was 71.5%; for those in a clinical risk group aged 6 months to 65 years old, the uptake was 48.5%; and for pregnant women, it was 43%. We have estimated influenza vaccine uptake using the coverage estimates published by Public Health England (PHE).[1]

There are a number of GP CMR systems in use; the systems eligible for use in English primary care must be part of GP System of Choice (GPSoC).[2] Practices have a single CMR system, which comprehensively contains data about their registered patients, their illnesses, therapy, and all the aspects of providing General Medical Services (GMS – the standard NHS

[1] Public Health England. Vaccine uptake guidance and the latest coverage data. https://www.gov.uk/government/collections/vaccine-uptake#seasonal-flu-vaccine-uptake

[2] Health and Social Care Information Centre. GP Systems of Choice (GPSoC)http://systems.hscic.gov.uk/gpsoc

primary care provision) or other primary care schema. There are predominantly 3 brands; the market leader is Egton Medical Information Systems (EMIS), followed by The Phoenix Partnership (TPP) SystmOne, and In Practice Systems (INPS) Vision.

These different systems have different data models, and our goal would be to be able to process data from all; in the first year, we would aim to have at least 2 out of these 3 data systems represented in our study, but this is dependent upon the practices that are willing to take part. These information systems broadly adopt 2 coding schemes (Read 2 and CTV3), but slightly different interfaces and preferred terms in the look-up tables. This may produce slightly different level of recording of codes, particularly non-QOF codes (Quality and Outcomes Framework

Ideally, GSKwould monitor only GSK vaccines. However, as this pilot study will help inform safety surveillance activities in subsequent years, we will initially collect data on any influenza vaccine administered in the study population. We will then stratify the analysis based on vaccine brand (GSK, 'other', unknown).

Inclusion/Exclusion criteria

As this is a population-based safety surveillance project, all individuals who receive influenza vaccination in the 9 GP practices between 1 September and 30 November 2015 are eligible for inclusion in the analysis. The 30 November cut-off is because EMA is primarily interested in signal detection and safety reporting early in the annual vaccination period. In the 3 practices additionally using the ADR card, this will be given to all subjects vaccinated or, as appropriate, a parent or carer.

In the database analysis, only registered patients who have explicitly opted out of data sharing will be excluded from the analysis. We will identify those opted out in 2 ways: (1) look for opt-out codes within GP information systems where the patients have made an explicit choice to opt out; and (2) post project information in practice websites and waiting areas or GP surgeries to inform patients of the project to give them the opportunity to ask questions and to opt out. In the active surveillance component, AE reporting rates will be stratified by total number of subjects given a card and those who returned the card. All subjects given a card will be included in the denominator when assessing response rate.

Data extraction and management

The method and governance procedure is developed by the [redacted] in partnership with [redacted] and PHE, using an approved provider, Apollo. Alternatively, we will use another approved data extraction supplier, or extract the relevant study data ourselves. Apollo extracts data using the Apollo automated extraction system. Communication is via a SOAP (Simple Object Access Protocol) web service, no special firewall configuration is needed.

Data extractions will be conducted in accordance with the Research Group's standard operating procedures in data extraction, pseudonymisation, and transfer. All data processing and analysis in the present proposed study will be conducted within the secure IT environment of the [redacted] at the [redacted] The information security policies and procedures of the Research Group have been approved by the NHS Health and Social Care Information Centre (HSCIC). Details of the departmental information governance policies and procedures can be found in:
http://www.clininf.eu/about/information-governance.html

We will only extract coded data, i.e. where the GP or other health professional codes a disease or symptom into the CMR system. The only exception to this are the regime and batch number fields of prescribing data. The latter may be important in identification of brand. The overwhelming majority of the large volume of research that has come out of UK primary care is based on coded data[3]. The richness of primary care data are such that we anticipate being able to detect important AEIs. At a future date, we may do free text analysis; however, ethical approval is difficult to obtain as it may contain personal details. It is not part of this protocol as the ethical approvals could not be obtained in time to begin data collection in 2015.

The following routinely collected patient data will be collected for the study:

- Demographic information: age, gender, ethnicity, registered date.
- Postcode: to understand any inequities in access according to level of social deprivation using Geographical Information System (GIS) methods. Full postcodes will be immediately transformed into deprivation scores, using the Index of Multiple Deprivation, within GP computer systems upon extraction.
- Primary care consultations following vaccination, any other markers of health care utilisation, and referral to further care.
- Reactogenicity outcomes of seasonal influenza vaccination as listed in the research literature and any contemporary EU guidance.
- Life-style/risk factors – e.g. BMI, smoking.
- Records of other diseases and long term conditions – e.g. chronic respiratory disease, chronic heart disease, chronic kidney disease, chronic liver disease, chronic neurological disease, diabetes, immunosuppression, pneumonia, etc.
- Pregnancy.

Once the data are extracted, they are transferred to the custom built Data Warehouse located within the N3 (NHSnet) or for analysis in secure networks that meet the NHS

[3] Kousoulis AA, Rafi I, de Lusignan S. The CPRD and the RCGP: building on research success by enhancing benefits for patients and practices. Br J Gen Pract. 2015 Feb;65(631):54-5. doi: 10.3399/bjgp15X683353.

Information Governance toolkit level 2 standard. Hosting for this data warehouse is by Daisy Group and managed by an established third party provider, Concentra (though we are testing systems that will remove Concentra from the process – with instead these data coming to [redacted]. These arrangements may change in the future in accordance with developments in technology.

At the point of the data drop, the data are filtered and proceed through a pseudonymisation package encrypting the NHS number. All data are strongly encrypted by a combination of symmetric and asymmetric encryption algorithms: Triple DES and RSA 1024 before transmission, and utilises public and private key pairs unique to each project. Pseudonymisation is applied at this stage to allow for backwards identification should there be a need to do so as part of an ethically approved study. However, the application of pseudonymisation at this stage also allows the same algorithm to be applied to additional data sources which may be linked data in future years, for example, enabling the linkage of patients' primary care and hospital data without a need to identify a person in the process of conducting this linkage.

A formal service level agreement (SLA) will be established with the volunteer practices, consenting to the use of their routinely collected data for the purposes of vaccine safety surveillance. This data will be extracted, stored, and processed by the team at the [redacted] and only aggregated tables will be made available in publications or to third parties.

Data analysis

R Studio within the secure analysis server is the analytical tool of choice for the Research Group. We will interpret coded data by the creation of ontologies that we will map to case-definitions, where available. However, we do not have the in depth descriptions required for case definition found, for example, in clinical trials. We will be inferring meaning from brief clinical coded information; though we have long experience of this and will have the opportunity to confirm with practices and practitioners how to interpret their clinical records.

Statistical analysis will consist primarily of reporting rates and proportions. Confidence intervals will be calculated; however, due to the effects of clustering and practice differences in this relatively small pilot these are likely to be wide.

Safety reporting, including routine pharmacovigilance

This study's primary endpoints are safety-related. However, it will be clearly communicated to participating practices that the study does not replace AEI reporting that would occur as part of routine practice; the reporting within this study is supplemental and their

participation should not alter routine safety reporting practices to either the appropriate authorities or MAHs in any way.

The team at [redacted] will review the data submitted weekly as part of the study. If the team at [redacted] becomes aware of a serious adverse event (SAE) experienced by a study participant, the SAE should be reported to GSK with 24 hours of awareness. If GSK deems additional information necessary, request of additional information will be sent through the team at [redacted] An SAE is defined as any untoward medical occurrence that:

- Results in death,
- Is life-threatening,
  NB: The term 'life-threatening' in the definition of 'serious' refers to an event in which the study participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.
- Requires hospitalization or prolongation of existing hospitalization,
- Results in disability/incapacity.
  NB: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza like illness, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Important medical events - events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the study participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

7.2 Project management

This study is conducted within the [redacted] formal frameworks for information and research governance. In addition, all externally funded projects and collaborative projects with external partners are supported and guided by the University's Research and Enterprise Support (RES) service. RES ensures that university-supported projects are financially viable, and that legal issues of knowledge transfer and intellectual properties are addressed. The project team is supported by IT services dedicated to the Faculty and to the Department of Health Care Management & Policy. Our secure analysis servers are optimised for routine healthcare data processing, to provide faster deliveries for our projects.

The project is accountable to the Project Steering Board, with the day-to-day operational issues managed by the Project Operational team.

Project Steering Board

The Steering Board will meet bi-annually to receive regular and exceptional reports, including reporting of adverse events, from the Operational Team, monitor progress against set milestones, and ensure that resources and support are available to enable the successful delivery of the project within the funding agreement. In the event of a report of adverse incidents, the Project Steering Board will co-ordinate an effective management of the adverse events in line with local and national guidance, and if appropriate, onward reporting to the University, GSK, external partners or external research and information governance authorities.

The Project Steering Board consists of senior academics from the [redacted] and collaborating universities, a patient representative, senior practitioners involved in the domain of influenza vaccine, and a representative of the GSK of the study.

Steering Board Member (TBD)	Role and Organisation
Prof [redacted]	Principal Investigator, [redacted]
	Research Representative, GSK
	Domain Expert, GSK
	GP/Practice representative
	Patient Representative
Dr [redacted]	Project Manager, [redacted]

Project operational team

The operational team is responsible for the completion of the project objectives against set milestones (see Section 5: Project Milestones), and submit regular and ad-hoc reports to the

Project Steering Board. The Team will meet fortnightly in person and/or via teleconference, particularly in the early stages of the project, to ensure the project meets with the milestones agreed for the project.

The Operation Team consists of research staff, the project manager and the Principal Investigator of this project:

Team Member (TBD)	Lead responsibility in the project and organisation
Prof [redacted]	Senior Clinical Lead, [redacted]
Dr [redacted]	Project Manager, [redacted]
	Research Representative, GSK
[redacted]	Research Fellow, [redacted]
[redacted]	Database developer, [redacted]
Dr [redacted]	Senior Research Fellow, [redacted]
[redacted]	Research Assistant, [redacted]

These arrangements are standard [redacted] research and surveillance governance requirements for projects.

Patient involvement

Patients will be involved in the protocol review from its completion. Their comments will be taken into consideration in the development of the protocol to help ensure its acceptability to patients. A patient representative will be part of the steering committee.

Practitioner involvement

Practices will be recruited from our existing research contacts and networks. We will look for practices purposefully to represent different social groups, brand of computerised medical record systems, and practice size (large practices may have more data extraction challenges).

Peer review of the study plan

The study plan will be sent for peer review by pharmacologists, general practitioners and lay advisors.

8. ETHICAL CONSIDERATIONS

The primary purpose of this study is to work with practitioners, governance experts, and a commercial MAH to develop robust process for the enhanced safety surveillance of seasonal influenza vaccines recommended by the EMA. The proposed study starts with an exploration of routinely collected primary care data from nine volunteer GP practices to assess if the data is fit for the purpose of supporting an enhanced EMA PASS of enhanced surveillance of seasonal influenza vaccination, and to draw conclusions if additional data collection in primary care is needed to meet EMA standards for enhanced surveillance of seasonal influenza vaccination.

The principal ethical issue is concerned with the protection and use of anonymised patient level information for the purpose of surveillance of safety of seasonal influenza vaccination as recommended by the EMA. NHS guidelines specify that a Section 251 approval is required when conducting research using anonymised patient level data, without individual level patient consent; approval is also dependent on the requesting institution meeting specific requirements on information governance, which the [redacted] exceeds. The protection and use of anonymised patient level information is addressed more fully in the next section: information governance considerations.

The [redacted] team will seek approval from the [redacted] In addition, the formal opinion of the Proportional Review System of the National Ethics Review Service will be sought regarding the need for [redacted] approval. 'Defining Research' (http://www.hra.nhs.uk/documents/2013/09/defining-research.pdf), the National Research Ethics Service (NRES) guidance suggests that surveillance does not require formal review by a Research Ethics Committee. The research team will however seek an opinion from the NRES's Proportional Review system to check if formal approval from a [redacted] is needed prior to the commencement of the study, as well as Section 251 approval.[4] If the proportional review suggests that a full [redacted] review is necessary, then applications will be submitted to the REC as well as the Clinical Research Network (CRN) and, if advised, the Confidential Advisory Group (CAG) for formal approval for Section 251 of NHS Act 2006 and Health Service (Control of Patient Information) Regulations 2002 exemptions.

Section 251 of the Health and Social Care Act 2001, allowed the Secretary of State to set aside the common law duty of confidentiality for defined medical purposes. Surveillance is generally taken to be one of the defined medical purposes for which data can be used. As it has not been tested whether the Health and Social Care Act is retrospective data are generally not extracted for periods prior to that Act, without a clear need generally approved by an ethics committee.

[4] Health and Social Care Act 2001. Section 251.
http://www.hra.nhs.uk/about-the-hra/our-committees/section-251/what-is-section-251/

Additionally, we will seek advice from NRES as to whether the individuals who are involved in the active surveillance portion of the study require formal taking of informed consent; or if collecting surveillance data in an anonymised form is acceptable.

9. INFORMATION GOVERNANCE CONSIDERATIONS

The [redacted] at the [redacted] has worked with routinely collected healthcare data in a number of research and evaluation projects over the last 15 years. The Research Group works within the research and Information Governance frameworks for health and social care in the United Kingdom, and is compliant with the University's best practice standards. The [redacted] is registered with the Information Commissioner's Office Data Protection Register, and is compliant with the Data Protection Act, and other legislations.

In addition, the Research Group reviewed its departmental information governance policies and procedures, against the requirements of the NHS Information Governance Toolkit (IGT) for Hosted Secondary Use Team/ Project, Version 12.[5] The review was approved by the Health and Social Care Information Centre, and was deemed satisfactory to support application to Confidentiality Advisory Group or the Data Access Advisory Group.

In line with the principle of the Data Protection Act 1998, data subjects will be informed of the uses of their data in this study. Participating GP practices will be asked to display project information in their website, and project information posters in reception areas, from when the practice has consented to take part in the study and until the study is completed.

The project information will specifically refer to the right of the patients to opt out if they do not wish their data to be included in this study. We will respect the codes in the data indicating that a patient does not wish to have their record available for research; we will, however, seek to report the number of patients within a practice who have chosen to opt out.

No strong patient identifiers (NHS numbers, postcodes, dates of birth, etc.) will be available to GSK, third parties, or in publications. Additionally, no patient level data will be sent to GSK in a way that the individual patient can be re-identified. This may involve GSK being blind to practice identities, and the locality at which any AEI occurs.

[5] Department of Health. Information Governance Toolkit. https://www.igt.hscic.gov.uk/

10. DISSEMINATION AND PUBLIC REGISTER DISCLOSURE

The outputs from the research will be disseminated primarily through peer review papers in high impact journals within the domains of primary care, surveillance, vaccines, and infectious diseases. We will present findings at relevant seminars and conferences.

The [redacted] in accordance with GSK policy, will post a summary of the study protocol and results within 12 months of study completion and following review and comment by GSK on GSK's Clinical Study Register, accessible at http://www.gsk-clinicalstudyregister.com and at www.clinicaltrials.gov.

11. SIGN OFF PAGE

For and on behalf of

GLAXOSMITHKLINE BIOLOGICALS S.A.

Date : 16 June 2015

Name : [redacted]

Title : EPIDEMIOLOGY DIRECTOR GSK Vaccines

For and on behalf of

[redacted]

Date : 15th June 2015

Name : [redacted]

Title : [redacted]

13. APPENDIX

Appendix 1

Data extraction is by automated routine as detailed below:

Currently, data are extracted by weekly bulk upload. Apollo extracts data using the Apollo automated extraction system. Communication is via a SOAP (Simple Object Access Protocol) web service, no special firewall configuration is needed.

Once the data are extracted, they are transferred using the above methodology to the custom built Data Warehouse located within the N3 (NHSnet) or for analysis in secure networks that meet the NHS Information Governance toolkit level 2 standard. Hosting for this data warehouse is by Daisy Group and managed by an established third party provider, Concentra. These arrangements may change in the future in accordance with developments in technology.

At the point of the data drop the data are filtered and processed through a pseudonymisation package encrypting the NHS number. All data are strongly encrypted by a combination of symmetric and asymmetric encryption algorithms: Triple DES and RSA 1024 before transmission, and utilises public and private key pairs unique to each project.

Pseudonymisation is applied at this stage to allow for backwards identification should there be a need to do so as part of an ethically approved study. However, the application of pseudonymisation at this stage also allows the same algorithm to be applied to additional data sources which may be linked data in future years; for example, enabling the linkage of patients' primary care and hospital data without the need to identify a person in the process of conducting this linkage.

12. REFERENCES

[i] European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC). Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU. London, EMA: Ref: EMA/PRAC/135943/2014; 06 March 2014. URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/03/WC500162574.pdf

[ii] Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC). URL: http://www.rcgp.org.uk/clinical-and-research/research-and-surveillance-centre.aspx

[iii] Workforce and Facilities Team, Health and Social Care Information Centre . General and Personal Medical Services: England 2003-13. 25 March 2014. URL: http://www.hscic.gov.uk/catalogue/PUB13849/nhs-staf-2003-2013-gene-prac-rep.pdf

[iv] The CMO announced the seasonal influenza vaccination programme for 2011/12 in a letter published 25 May 2011 available to view and download from the DH website: https://www.gov.uk/government/publications/the-seasonal-flu-immunisation-programme-2011-12--2

[v] David A. Asch M.Kathryn Jedrziewski, Nicholas A. Christakis, Response rates to mail surveys published in medical journals Journal of Clinical Epidemiology Volume 50, Issue 10, October 1997, Pages 1129–1136

[vi] MRC Policy and Guidance on Sharing of Research Data from Population and Patient Studies (Sept 2011) http://www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/datasharing/Policy/index.htm

[vii] Economic Co-operation and Development (OECD). "Promoting Access to Public Research Data for Scientific, Economic and Social Development" 2007 http://www.oecd.org/sti/sci-tech/38500813.pdf

GlaxoSmithKline Biologicals
Vaccine Value and Health Science
Sponsor Signatory Approval Page

Please note that by signing this page, you take responsibility for the content of the Study Report, including appendices

STUDY TITLE: Enhanced safety surveillance (ESS) of seasonal influenza vaccines: feasibility study

Study: 202055 (EPI-FLU-045 VS UK) Development Phase: NA

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory: [redacted]

Title of Sponsor Signatory: Director, Epidemiology

Signature: [redacted]

Date: 17/02/2016