| | |
|---|---|
| **Title** | Post-licensure observational safety study of specific outcomes after Optaflu vaccination among adults in The Health Improvement Network (THIN) database of routine UK primary care records |
| **Version identifier of the final study report** | Version 1 |
| **Date of last version of the final study report** | Not applicable |
| **EU PAS registry number** | ENCEPP/SDPP/4101 |
| **Active substance** | cTIV |
| **Medicinal product** | Optaflu |
| **Product reference** | V58_30OB |
| **Procedure number** | EMEA/H/C/758/FUM (MEA 041.1) |
| **Marketing authorization holder(s)** | Novartis Influenza Vaccines Marburg GmbH |
| **Joint PASS study** | No |
| **Research question and objectives** | To investigate the safety of cTIV vaccination in adults in routine clinical care in the UK with regard to pre-specified outcomes:<br>To report and plot the number of study outcomes pre- and post-vaccination in outcome specific pre-defined time windows in relation to the date of vaccination. When events are identified in a high risk post-exposure window, to provide a ratio of observed to expected rates.<br>To report the incidence of study outcomes in the six months after vaccination. |
| **Country(ies) of study** | UK |



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| | |
|---|---|
| **Author** | Gillian Hall,<br>Gillian.hall@gchall.com<br>Grimsdyke House, EN5 4ND, UK<br>Office: 44 (0) 20 8441 8421<br>Mobile: 44 (0) 7939278216 |

**Marketing authorization holder(s)**

| | |
|---|---|
| **Marketing authorization holder(s) details** | Novartis Influenza Vaccines Marburg GmbH |
| **MAH contact person** | José van Boxmeer<br>Epidemiology, Seqirus, Hullenbergweg 89, 1101 CL Amsterdam, The Netherlands<br>Email: jose.van_boxmeer@seqirus.com |

**This study was conducted according to the Guidelines for Good Pharmacoepidemiology. This report was prepared in accordance with STROBE guidelines with EMA's Guidelines on Good Pharmacovigilance Practices (Module VIII post authorization safety studies)**

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**May not be divulged, published, or otherwise disclosed without written consent of Seqirus.**



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# 1. ABSTRACT

| Name of MAH: | Study number: | Date of Report Abstract: |
|---|---|---|
| Novartis Influenza Vaccines Marburg GmbH | V58_30OB | 29 JUN 2016 |

**Title of Study:** Post-licensure observational safety study of specific outcomes after Optaflu vaccination among adults in The Health Improvement Network database of routine UK primary care records

**Keywords:** Influenza vaccination, safety, neurology, immunology

**Rationale and Background:** This post authorization safety study was committed to the European Medicines Agency (EMA) at the time of marketing authorization for Optaflu® in 2007. Optaflu® is a subunit influenza vaccine that is not produced in embryonated hen eggs, but in a suspension of a specific cell line cloned from Madin Darby Canine Kidney tissue. The cell culture trivalent influenza vaccine (cTIV) is a sterile preparation of purified influenza antigens in an isotonic buffer solution for intramuscular administration. The final product contains the membrane proteins hemagglutinin and neuramidase as active ingredients. As recommended by the World Health Organization, these proteins are derived from three influenza virus strains (A/H1N1, A/H3N2 and B). The study investigates the safety of cTIV in a large population of adults vaccinated as part of routine primary care. The new safety data will be added to the existing evidence from the clinical database. The study outcomes are anaphylactic reactions and angioedema, Bell's palsy, neuritis (optic and brachial), convulsions, demyelination, thrombocytopenia, paraesthesia and inflammatory bowel disease (IBD), including Guillain-Barré syndrome (GBS), non-infectious encephalitis and vasculitis. These outcomes were selected on the basis of previous documented data of an increased risk after exposure to other influenza vaccines, or were rare events stated to have been caused by influenza vaccination in case reports in the literature. With the exception of thrombocytopenia, paraesthesia and IBD, the outcomes were included in a specific guidance regarding pandemic influenza vaccines (European Medicines Agency Committee for Medicinal Products for Human Use, 2009). No additional outcomes for further investigation have been suggested by existing clinical data or other information.

**Research Question and Objectives:** To investigate the safety of cTIV vaccination in adults in routine clinical care in the UK with regard to pre-specified incident outcomes:

- To report and plot the number of study outcomes pre- and post-vaccination in outcome specific pre-defined time windows in relation to the date of vaccination.



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When events are identified in a high risk post-exposure window, to provide a ratio of observed to expected rates.

- To report the incidence of study outcomes in the six months after vaccination.

**Study Design:** The study was an observational, retrospective, post-marketing safety study of cTIV use in routine UK care based on secondary data.

The study population, exposure and outcomes were identified from the The Health Information Network (THIN) database. THIN is an observational database of pseudonymised UK electronic primary healthcare records. This analysis reports results from three influenza vaccination seasons (from 2012 to 2015).

An algorithm to identify IBD exacerbation and multiple sclerosis (MS) relapse was developed in the third season of the study and validated against a practice questionnaire.

**Setting:** Data from UK primary care.

**Subjects and study size:** The study population comprised patients who were exposed to cTIV between September to March in any of the three influenza vaccination seasons (from 2012 to 2015) while over 18 years of age and permanently registered with the practice on the date of vaccination and for the previous 12 months.

The study was planned as a hypothesis generating study. A sample size of 9000 exposures was designed to rule out outcomes occurring with a frequency of 1 in 3000 if no outcome was observed. This basis was used because most of the study outcomes are rare so no outcomes might have been identified in the post-exposure risk-windows.

As this study was completed on the THIN database, the number of exposures available for inclusion was dependent on the use of cTIV in the THIN population during seasonal vaccination periods included in the study. This report includes data from a total of 4578 exposures. The planned sample size of 9,000 was not reached because cTIV (Optaflu) marketing was discontinued.

**Variables and data sources:**

**Data Source(s):** The study population, exposure and outcomes were identified from practices within THIN database. THIN is an observational database of pseudonymised UK electronic primary care patient records. Within the electronic patient record the practice staff routinely record details of medical events, treatments and any preventive medicine. This includes recording of the date, type and batch number of vaccinations as they are administered. A pre-study feasibility assessment has shown that batch numbers or brand name can be identified for more than 90% of seasonal influenza vaccinations in the THIN database (Hall et al. 2013).



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**Exposure(s) of interest**

The exposure of interest was vaccination with cTIV (Optaflu). Exposure was identified by the brand or batch number documented against an influenza vaccination entry in a THIN database patient record. Batch numbers were compared to those for cTIV supplied to the UK.

**Outcome(s)**

Incident diagnoses of the following outcomes were identified from the THIN database:

- Anaphylactic reactions, and severe angioedema (severe allergic reactions)
- Bell's palsy
- Convulsions
- Demyelination in total and Guillain-Barré syndrome (GBS) alone
- Paraesthesia
- Non-infectious encephalitis
- Neuritis (optic and brachial)
- Vasculitis
- IBD
- Thrombocytopenia

Two case definitions, including definition for assigning the date of onset, were developed for each outcome, a primary case definition and a stricter, study case definition. The primary case definition for most outcomes required documentation that a new diagnosis was made or confirmed in secondary care. Exceptions included Bell's palsy, convulsions and giant cell arteritis (a form of vasculitis) which can be diagnosed in primary care alone. For these outcomes, a diagnosis made in primary care was sufficient. The primary case definition of thrombocytopenia included all those which matched the study case definition (which could be based on clinical data alone) as well as those with diagnosis made or confirmed in secondary care. The study case definition was applied to each outcome in a sensitivity analysis to minimize differential misclassification, see 10.3 Outcome Data for more detail. This study case definition excluded cases with identified alternative explanations and was in line with other published definitions (such as the Brighton Collaboration definitions), when this was feasible using primary care records.

The period of observation was from three months before to six months after the date of exposure for that person. Outcome specific risk-windows were defined based on the biologically plausible time frame when an outcome caused by the vaccine might be expected to occur (the high risk-window). For convulsions, paraesthesia and GBS a second, high risk-window was defined either because these reflected different types of



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outcome (such as febrile and other seizures) or because the most appropriate window was not clear from the literature. A low risk-window immediately before exposure was also defined for each outcome. This was the period of time that someone with the outcome might delay vaccination and was excluded from the analyses to avoid a 'healthy user' effect.

Possible outcomes were initially identified from THIN by searching for Read or drug codes (NHS Centre for Coding and Classification, 1996), and key terms in unstructured text. The details of each of these possible outcomes were reviewed against the two case definitions by an Adjudication Committee and categorized as a case or not, and with a date of onset for outcomes. A flow chart of case ascertainment is given at the end of Section 9.5 and the role of the Adjudication Committee is described there and in Section 9.4.2.

In addition to the incident outcomes listed above, the Adjudication Committee developed case definitions and algorithms with the objective of identifying IBD exacerbations and relapses of MS from THIN (Section 9.4.2). The algorithm included a combination of clinical events and episodes of treatment. The algorithm was validated against a practice questionnaire during the third study season to determine its performance.

**Other variables:** Details of age, sex, and chronic diseases were obtained from the THIN database. Administration of concomitant pneumococcal polysaccharide vaccine was also identified.

**Results:** The 4578 exposures to cTIV were identified across three seasons 2012-2013 (n=623), 2013-2014 (n=2106) and 2014-2015 (n=1849). Further seasons were not included as the cTIV (Optaflu) was no longer available on the market. The mean age of the population at exposure was 60.5 years (SD 16.5), 42.6% were male and 56.9% had a history of one or more chronic illness with which influenza vaccination is recommended. The mean period of observation including pre- and post- exposure time was 272 days. Pneumococcal polysaccharide vaccination within 28 days of cTIV was recorded for 4.6% of exposed people.

Sixteen outcomes fulfilled a primary case definition within the observation period (see Table 1 below). No neuritis (optic or brachial), non-infectious encephalitis or first central nervous system demyelinating event was identified. Three of the 16 outcomes (convulsion, thrombocytopenia and IBD) occurred within the high risk-window for that condition. One of four convulsions was dated during the later high risk-window defined for that outcome (8 – 30 days after cTIV exposure) and three were in the expected window with an observed to expected ratio of 3.3, (95% confidence intervals (CI) 0.3, 31.7). One of five thrombocytopenia outcomes was in the high risk-window, and three were in the expected time with an observed to expected ratio of 1.5 (95% CI 0.2, 14.9). The remaining thrombocytopenia was in the pre-exposure low-risk period, which was



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excluded from the calculation. The convulsions and thrombocytopenia in the high risk-window fulfilled only the primary case definition. The one IBD outcome had a date of onset within the high risk period and fulfilled both the primary and study case definitions. It was not possible to calculate an observed to expected ratio as there were no IBD outcomes in the expected time. The remaining outcomes occurred outside the high risk-window and were one Bell's palsy, one severe allergic reaction, two vasculitis, and two paraesthesia. The incidence rates for each of the outcomes in the six months observation following vaccination are presented in the Table below.

In the third season 49 (2.7%) people with prevalent IBD and 18 (1.0%) with MS were identified from the overall THIN cohort. The PPV for IBD exacerbations identified from THIN against 30 returned questionnaires was 0.1 (95%CI 0.01, 0.46). No PPV was estimated for MS relapse, as only two episodes were reported on 13 practice questionnaires. Neither of these was identified from THIN. It was concluded that the identification of IBD exacerbations and MS relapses on the basis of the algorithm did not perform well enough to be run across the total study population.

**Table: By outcome: the total number, number in the high risk-window, observed to expected and incidence in the six months after cTIV exposure, using the primary case definition**

| Outcome | Outcomes during total observation period | Outcomes in the high risk-window N, observed to expected (95% CI) | Incidence per 100,000 person years (95% CI) in the 6 months post exposure |
|---|---|---|---|
| Bell's palsy | 1 | 0 | 44.1 (6.2, 313.1) |
| Convulsions | 4 | 1, 3.3 (0.3, 31.7) | 132.4 (42.7, 410.4) |
| Thrombocytopenia | 5 | 1, 1.5 (0.2, 14.9) | 132.3 (42.7, 410.3) |
| Severe allergic reaction | 1 | 0 | 44.1 (6.2, 313.1) |
| Vasculitis | 2 | 0 | 88.2 (22.1, 352.8) |
| IBD | 1 | 1* | 44.1 (6.2, 313.2) |
| Paraesthesia | 2 | 0 | - |
| Demyelination | 0 | 0 | - |
| Non-infectious encephalitis | 0 | 0 | - |
| Neuritis (Optic and Brachial) | 0 | 0 | - |

*No 'observed to expected' could be calculated, as there was no event outside the high risk-window.



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**Discussion:**

This was a hypothesis generating study, which included 4578 cTIV exposures. There was no Bell's palsy, severe allergic reaction, vasculitis, paraesthesia, demyelination, non-infectious encephalitis or Neuritis (optic and brachial) found within the high risk-window. For three outcomes, convulsion, thrombocytopenia and IBD a single event in the high-risk window was identified. The observed versus expected ratios for these outcomes were above one. However, the confidence intervals were wide, included one and were based on single events in the high risk-window and few episodes in the expected window. No observed to expected could be calculated for IBD as the only event was in the high risk-window. The incidence rate of IBD in the six months after exposure did not indicate an increased risk when compared to other published rates.

In conclusion, although the sample size was too small to rule out associations, the results from this general population study have not generated a hypothesis of an increased risk of the selected study outcomes after vaccination with cTIV.

**Marketing Authorization Holder(s):**

Novartis Influenza Vaccines Marburg GmbH

**Names and affiliations of principal investigators:**

Gillian Hall, Gillian Hall Epidemiology Ltd.



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## 2. LIST OF ABBREVIATIONS

| | |
|---|---|
| ADEM | Non-infectious acute disseminated encephalomyelitis |
| AESI | Adverse events of special interest |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence Intervals |
| CSD | Cegedim Strategic Data Medical Research Ltd |
| cTIV | Cell culture trivalent influenza vaccine |
| EMA | European Medicines Agency |
| GBS | Guillain-Barré syndrome |
| IBD | Inflammatory bowel disease |
| MS | Multiple sclerosis |
| NPV | Negative predictive value |
| NVD | Novartis Vaccines and Diagnostics |
| PASS | Post Authorization Safety Study |
| PPV | Positive predictive value |
| THIN | The Health Information Network |
| UK | United Kingdom |



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## 3. INVESTIGATORS

Principal Investigator: Gillian Hall PhD. Grimsdyke House, Ravenscroft Park, Barnet, London, EN5 4ND, UK

## 4. OTHER RESPONSIBLE PARTIES

**Marketing Authorization Holder Study Contacts**

Observational Study Leader/ Epidemiologist:

José van Boxmeer, Epidemiologist, Seqirus.

Hullenbergweg 89, 1101 CL Amsterdam, The Netherlands.

Of note: On 02 Mar 2015, Novartis AG divested its global Vaccines business (excluding influenza vaccines). Thereafter, its influenza vaccines business commenced business as Novartis Influenza Vaccines (abbreviated to NIV).

On 31 Jul 2015, CSL Ltd. closed its acquisition of Novartis AG's influenza vaccines business, and business commenced as NVS-IV, now owned and operated by the CSL group. On 09 Nov 2015, the combined flu business of NVS-IV and bioCSL started operating under the global brand Seqirus.

### 4.1 Main contributors to the observational study report

Principal Investigator: Gillian Hall

Data management: IMS Health Ltd. 210 Pentonville Road London, N1 9JY.

Statistician: Caroline O'Leary, Senior Consultant, Data Science Real-World Evidence Solutions

### 4.2 Contract Research Organization

Caroline O'Leary, Senior Consultant, Data Science Real-World Evidence Solutions, IMS Health Ltd. 210 Pentonville Road London, N1 9JY.

IMS Health Ltd. was responsible for the THIN data, programming and quality assurance of the data cut and for the statistical analysis of the data for the main study.

Cegedim Strategic Data Medical Research Ltd (CSD), 1 Canal Side Studios, 8-14 St Pancras Way, London NW1 0QG, England) was responsible for these tasks until IMS took over CSD and the contract in the third study season.



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### 4.3 Advisory Committee

An Adjudication Committee comprised the Principal Investigator,

Paul Davies, Consultant Neurologist, Northampton General Hospital NHS Trust,

Cliftonville, Northampton NN1 5BD, UK, and

Yousuf Karim, Consultant Immunologist, Royal Surrey County Hospitals Guildford GU2 7XX, UK.

The Adjudication Committee's responsibilities:

- To agree study outcome case definitions and risk windows (pre- and post exposure).
- To agree a strategy to identify outcomes including the Read code lists for the initial search. This included both the initial study outcomes and IBD exacerbations and MS relapses.
- To review cases of new outcomes against the outcome definitions and to identify new episodes and assign a date of onset. Cases were reviewed against both the primary and study case definition and classified as a primary outcome only or both a primary and study outcome.
- To review the results of the IBD exacerbations and MS relapses validation exercise and to agree on the decision as to whether the algorithm should be run across all study years (see Section 9.4.2).
- The Adjudication Committee was also required to agree with the study results and interpretation.



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# 5. STUDY MILESTONES

## Table 5-1 Overview of study milestones

| Milestone | Planned date (DDMMMYY) | Actual date (DDMMMYY) |
|---|---|---|
| Start of data collection | 16JUL2013 | 20AUG2013 |
| End of data collection | 9000 exposed patients | 07JUN2016 |
| Interim report 1 | 28APR2014 | 22APR2014 |
| Interim report 2 | 31MAY2015 | 18MAY2015 |
| Registration in the EU PAS register | 19JUL2013 | 04JUL2013 |
| Approval from Ethics Committee/Institutional Review Board | NA | Version 2: 18JUN2013<br>Version 3 with exacerbations / relapses: 17NOV2014 |
| Final report of study results | Based on number of exposed | Please see Report issue date. |



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## 6. BACKGROUND AND RATIONALE

Influenza is a highly contagious acute viral infection that affects people of all ages. Most people recover in a week or two, but influenza can cause serious morbidity and mortality, particularly among vulnerable individuals including the elderly and those with pre-existing chronic disease (Neuzil et al. 1999; McBean et al. 2004). Influenza epidemics occur mainly in the winter in the Northern hemisphere and can result in widespread disruption to healthcare and other services. A vaccine is produced every year based on the strains of virus expected to be circulating. Vaccination against seasonal influenza is recommended for at risk groups including the elderly, those at-risk because of chronic disease and people living in long-stay residential care homes. Influenza vaccination has been shown to reduce the number of hospitalizations and deaths due to respiratory disease (Mangtani et al. 2004).

The cell culture trivalent influenza vaccine (cTIV), Optaflu® is a vaccine that was filed for registration with European Medicines Agency in 2007 for use in adults over the age of 18 years. cTIV is no longer produced in embryonated hen eggs, but in a suspension of a specific cell line cloned from Madin Darby Canine Kidney tissue. The influenza cell culture subunit vaccine (cTIV) is a sterile preparation of purified influenza antigens in an isotonic buffer solution for intramuscular administration. The final product contains the membrane proteins hemagglutinin and neuramidase as active ingredients. As recommended by the World Health Organization, these proteins are derived from three influenza virus strains (A/H1N1, A/H3N2 and B).

The safety of cTIV has been evaluated in twelve completed clinical studies, all randomized controlled clinical trials, with 7972 adult and 2264 pediatric subjects who received at least one dose of cTIV. No potential safety concerns were raised by the European Medicines Agency (EMA) based on these data. In the past, studies of other seasonal influenza vaccinations have shown an increased risk of Bell's palsy, Guillain-Barré syndrome (GBS), paraesthesia and inflammatory bowel disease (IBD (Mutsch et al. 2004; Juurlink et al. 2006; Bardage et al. 2011). Case reports and case series have suggested rare causal associations between influenza vaccinations and neuritis, allergic reactions, non-infectious encephalitis, thrombocytopenia and vasculitis (Hull et al. 2004; Peng et al. 2004; Hjalmarsson et al. 2009; Zafrir et al. 2009; Mantadakis et al. 2010). Recommendations for pharmacovigilance plans for pandemic influenza vaccines by the EMA's Committee for Medicinal Products for Human Use (CHMP) list biologically plausible adverse events of special interest (AESI) and recommends a post-authorization safety study that follows exposed subjects for at least six months after the last dose of vaccine (European Medicines Agency Committee for Medicinal Products for Human Use 2009). These AESI are anaphylactic reactions and angioedema, Bell's palsy, convulsions, demyelination including Guillain-Barré syndrome (GBS), neuritis, non-infectious encephalitis and vasculitis. Influenza vaccination has also been reported to increase the risk of narcolepsy (Bardage et al. 2011) however, as the increased risk was in children



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and adolescents it was not included as an outcome in this study of adults. The possibility of including syncope was reviewed but it was concluded that a general practice database is not an appropriate data source to investigate this as an outcome. If a patient faints, it will not always be reported to the GP. If syncope is more likely to be reported to the GP after a vaccination, this could introduce bias. The EMA has also expressed an interest in the safety of vaccinations in people with prevalent multiple sclerosis (MS) and IBD. An additional analysis was therefore added to season three of the study to investigate relapse of MS and exacerbation of IBD after cTIV exposure. We found no evidence in the literature or elsewhere that these events had been studied using electronic health care records so an initial validation step was included.

The primary purpose of this study was to investigate the safety of cTIV in routine post-marketing use in the UK with regard to serious biologically plausible outcomes. Anaphylactic reactions and angioedema (severe allergic reactions) Bell's palsy, convulsions, demyelination including GBS, neuritis (optic and brachial), non-infectious encephalitis, thrombocytopenia, vasculitis, paraesthesia and IBD were studied.

## 7. RESEARCH QUESTION AND OBJECTIVES

To investigate the safety of cTIV vaccination in adults in routine clinical care in the UK with regard to pre-specified outcomes:

- To report and plot the number of study outcomes pre- and post-vaccination in outcome specific pre-defined time windows in relation to the date of vaccination. When outcomes are identified in a high risk post-exposure window, to provide a ratio of observed to expected rates.
- To report the incidence of study outcomes in the six months after vaccination.



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# 8. AMENDMENTS AND UPDATES TO THE PROTOCOL

## Table 8-1 Overview of protocol amendments and updates

| Number | Date | Section of the study protocol | Amendment or update | Reason |
|---|---|---|---|---|
| 1 | 04Apr2013 | All | Updated format. Study design was not changed. | New NVD study protocol template approved on Nov 27th, 2012 |
| | | 4.0 Abstract and 9.3.1 Exposure sections | Addition of feasibility study results | Exposure feasibility study completed |
| | | 9.5 Study size | Update to study numbers and so timelines | New sales estimates from NVD |
| | | Appendix 1 | Addition of ENCePP checklist | New requirement based on PV guidance EMA/813938/2011 (Guideline on Good Pharmacovigilance Practices (GVP), Module VIII – Post authorization safety studies, 2012) |



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| Number | Date | Section of the study protocol | Amendment or update | Reason |
|---|---|---|---|---|
| 2 | 29AUG2014 | Multiple sections | Inclusion of exacerbation of IBD and MS relapse as outcomes. Additional risk window of 1 to 60 days was included for GBS.<br><br>Inclusion of a third season and possibility of a fourth season.<br><br>Administrative updates | Request by the CHMP.<br><br>Projected feasibility of achieving a sample size of 9000 based on the total number of exposed available for the 2012 – 2013 and 2013 – 2014 seasons |

The protocol states that 'Primary case definitions will include all outcomes diagnosed in secondary care, except for seizures and Bell's palsy which are diagnosed by the primary care physician in some cases' and later qualified this by stating that the role of the Adjudication Committee included 'To agree study case definitions and risk windows'. The Adjudication Committee has agreed that the primary case definition of vasculitis should include a case of giant cell arteritis diagnosed in primary care provided this was supported by evidence of an appropriate treatment plan and resolution of symptoms. This adjustment was not a deviation from the protocol since the protocol later states that the role of the Adjudication Committee included 'To agree stricter study outcome case definitions and risk windows'.

Of note, Annex 2 to this report gives the case definitions, code lists and risk windows defined by the Adjudication Committee. These specifications were developed before the first interim report in April 2014. Several clarifications to the first interim report case definitions were made in season 2 in addition to the vasculitis case definition discussed in the last paragraph. These include:

- The definition of convulsions was clarified to exclude cases with clear evidence of a seizure due to an overdose of a drug, which is known to cause convulsions.
- It was recognized by the Adjudication Committee that platelet counts are not necessarily routinely measured in primary care and there may be a gap of several years between measurements. The thrombocytopenia case definition was therefore amended to allow inclusion of events where the previous count was $<150\times10^9$ $L^{-1}$



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if there was evidence that the event was a new episode of thrombocytopenia. It was stated in the case definition that events fulfilling the study case definition were also included as primary cases.

- Microcolitis was included in both case definitions of IBD.

All case definitions in Annex 2 A have been applied consistently across the study seasons.



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# 9. RESEARCH METHODS

## 9.1 Study Design

The study was an observational, retrospective, post-marketing safety study of cTIV use in routine UK care.

## 9.2 Setting

The study included data from people exposed to cTIV across three influenza vaccination seasons, September to March 2012 – 2013, 2013 – 2014 and 2014-2015. Study outcomes with onset from three months before the date of cTIV vaccination to six months afterwards were included in the analysis (the observation period).

## 9.3 Subjects

### 9.3.1 Source population

The source population was UK primary care. The database population was the THIN database. The study population, vaccine exposure, study outcomes and patient characteristics were identified from THIN practices. In summary, THIN is an observational database of pseudonymised electronic medical records from primary care practices throughout the UK. The database therefore provides information on safety during usual care in the general population. Details of demographics and administrative data, primary care diagnoses and prescription treatment are routinely recorded against date in separate files within individual patient records. Secondary care diagnoses and deaths are also captured because of the structure of the UK health service where primary care physicians act as 'gatekeepers' to secondary care. Major events from before computerization are added retrospectively. Data on preventive medicine can be recorded including details of any vaccinations. In the UK, the majority of influenza vaccinations are given by primary care practitioners. The practice staff can record vaccinations given and batch number. Medical events are automatically coded at entry using the Read clinical coding system (NHS Centre for Coding and Classification, 1996). Additional information is often available as text linked to the coded fields including electronic or scanned discharge summaries. Details of preventive medicine and laboratory results are included in the Additional Health Data file. It should be noted that for many practices, the electronic record is the primary record and there is no paper version for comparison.

Consequently, THIN provides the advantages of being an observational general population database covering approximately 6% of the UK population. The THIN records reflect routine practice and use of vaccines.



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UK electronic primary care records have previously been used for the study of the safety of vaccines (Kaye et al. 2001; Tata et al. 2003) including influenza vaccines (Smeeth et al. 2004; Stowe et al. 2009).

### 9.3.2 Inclusion and exclusion criteria for the study population

The study population comprised all people 18 years of age and over permanently registered at a THIN study practice for at least 12 months with a record that they had received at least one dose of cTIV vaccine as a seasonal influenza vaccination between September and March inclusive 2012 – 2013, 2013-2014 and/or 2014 - 2015.

### 9.3.3 Informed consent

No informed consent was obtained as the electronic records are pseudonymised; that is the identities of patients and practices are not known to researchers. A feedback method has been developed via a third party to allow validation without breaking this pseudonymization.

## 9.4 Variables

### 9.4.1 Exposure of Interest

The exposure of interest was cTIV (Optaflu) vaccination used as a seasonal vaccination in routine clinical care by primary care professionals. In the UK, vaccination against seasonal influenza is recommended between October and March for at risk groups.

Within the adult population (18 years and older) those aged 65 and over, pregnant women and those in a clinical risk group are offered influenza vaccination annually within the UK NHS (http://www.nhs.uk/Conditions/vaccinations) The clinical risk groups include anyone with chronic respiratory, heart, kidney, liver or neurological disease, immunosuppression or diabetes. Those living in long-stay residential care homes, people who are the main carer of someone whose welfare may be at risk if the carer falls ill, and all frontline health and social care workers are also offered flu vaccination. In the UK, most seasonal influenza vaccinations are given to at-risk groups by their primary care physician.

### 9.4.2 Outcomes

The study outcomes comprised the incident episodes of the conditions listed below:

Allergic reactions:

- Anaphylactic and anaphylactoid reactions, and severe angioedema (severe allergic reactions)



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Neurological:

- Bell's palsy
- Convulsions
- First central nervous system demyelinating event (including Guillain-Barré syndrome (GBS), non-infectious acute disseminated encephalomyelitis (ADEM), multiple sclerosis, Schilder's disease, transverse myelitis and other demyelinating disease of CNS)
- GBS alone
- Paraesthesia
- Non-infectious encephalitis
- Neuritis (optic and brachial)

Autoimmune:

- Vasculitis
- Inflammatory bowel disease (IBD) - incident

Hematological:

- Thrombocytopenia

These have been identified as biologically plausible outcomes following vaccination by the CHMP and in other safety studies.

Two case definitions for each outcome (including date of onset) were developed by the Adjudication Committee (Annex 2). The primary definition required a secondary care diagnosis for most outcomes. The exceptions were Bell's palsy, giant cell arteritis (a form of vasculitis) and convulsions, which can be diagnosed by a primary care physician. A firm or well described primary care diagnosis was accepted for these outcomes. The primary case definition of thrombocytopenia included all those which matched the study case definition (which could be based on clinical data alone) as well as those with diagnosis made or confirmed in secondary care. The study case definition excluded cases with identified alternative explanations and was in line with other published definitions (such as the Brighton Collaboration definitions) when this was feasible using primary care records. It is possible that differential misclassification will occur in cases diagnosed immediately after vaccination if it is known that a condition has been associated with vaccinations in the past, for example in GBS. The sensitivity analysis using the study case definitions was included to reduce this bias. Thrombocytopenia after recent chemotherapy or radiotherapy was an exclusion criterion in both case definitions for this outcome because of potential bias. It is well documented that these treatments increase the risk of



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thrombocytopenia. They are also likely to decrease the chance of vaccination during therapy due to both clinical and social factors.

Lists of Read codes and text terms, which could identify the outcomes, were compiled with the Adjudication Committee (Annex 2 Table A4). In season 1, the Read dictionary did not have an entry for anaphylaxis. In all seasons, codes for an allergic reaction were identified if there was no code indicating that this was not anaphylaxis (for example allergic rhinitis) as well as searching for terms suggesting anaphylaxis. Prescriptions for adrenaline injections were also identified, as were the initiation of aminosalicylate treatment for the identification of IBD. An identified platelet count of $<150\ 10^9$/L was reviewed for thrombocytopenia.

High risk-windows for each outcome were defined by the Adjudication Committee (Table 1). The high risk-window was a biologically plausible period when an outcome could be associated with cTIV exposure and was based on time between the exposure and outcome observed in published observational studies, passive surveillance or case reports. For example, an appropriate high risk-window for severe allergic reactions is 1-2 days as this outcome occurs very quickly after exposure to the allergen while an autoimmune condition is less likely to occur in the first days after exposure to a causal agent, but can present several weeks later. For convulsions, paraesthesia and GBS more than one high risk-window was defined either because these reflected different types of outcome (such as febrile and other convulsions) or because the most appropriate window was not clear from the literature. The high risk-window for paraesthesia started at day seven. This starting day was used to exclude injection site reactions, which, by definition, can only occur immediately after vaccination. Injection site reactions are not the intended outcome.

A low risk-window immediately before exposure was also defined for each outcome by the Adjudication Committee. This low risk-window was the period of time that someone with the outcome might delay vaccination and was excluded to avoid a 'healthy user' effect in the analysis (Section 9.9.2).



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**Table 1: Post-exposure high, and pre-exposure low, risk windows by outcome (exposure = day 0)**

| Outcome | High risk-window number | High risk-window (days)* | Pre-exposure low risk-window (days)§ |
|---|---|---|---|
| Severe allergic reactions | One high risk-window | 0 – 1 | -14 – -1 |
| Bell's palsy | One high risk-window | 1 –90 | -60 – 0 |
| Convulsions | | | |
| | High risk-window 1 | 0 – 7 | -14 – -1 |
| | High risk-window 2 | 8 – 30‡ | -14 – -1 |
| First central nervous system demyelinating event† | One high risk-window | 0 – 60 | -90 – -1 |
| GBS | | | |
| | High risk-window 1 | 7 – 60‡ | -90 – 0 |
| | High risk-window 2 | 1 – 60 | -90 – 0 |
| Paraesthesia | | | |
| | High risk-window 1 | 7 – 42‡ | -14 – 0 |
| | High risk-window. 2 | 43 –77‡ | -14 – 0 |
| Non-infectious encephalitis | One high risk-window | 1 – 60 | -14 – 0 |
| Neuritis, (optic and brachial) | One high risk-window | 1 – 42 | -30 – 0 |
| Vasculitis | One high risk-window | 1 – 30 | -90 – 0 |
| Inflammatory bowel disease | One high risk-window | 0 – 42 | -30 – -1 |
| Thrombocytopenia | One high risk-window | 0 – 42 | -30 – -1 |

GBS: Guillain-Barré syndrome.

* Outcomes with onset within this high risk-window are 'observed' cases while outcomes with a date of onset outside this window are 'expected'

§Excluded from the analyses to avoid a 'healthy user' effect. Also see Figure 2.

†Includes GBS

‡Time between exposure (day 1 except for convulsions when day 2) and high risk window start is excluded.

In addition to above incident outcomes, IBD exacerbation and MS relapse were investigated as outcomes during the third season of this study. Due to the nature of these events, and the fact that there was little data on identification of exacerbations from electronic primary healthcare records, the process of identification differed to that of incident outcomes and a validation exercise was conducted before any other analysis was attempted. Case definitions were developed by the Adjudication Committee to identify exacerbations in people with prevalent IBD and, separately, relapses in MS patients (Annex A Table A2). These definitions were programmed as algorithms to interrogate THIN and run on the sub-groups of patients with a record of prevalent disease. The details of the algorithms are given in (Annex A Table A2). The IBD exacerbation algorithm included searches for records of specific symptoms and treatments, or



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combinations of IBD, less specific symptoms or treatments, or a referral. MS relapses were identified by searching THIN for records of specific diagnoses or symptoms, or combinations of MS, less specific symptoms, treatments and disease history. The results of the THIN analysis were validated against a practice questionnaire (9.10 Quality Control). In addition, the Adjudication Committee agreed the risk-windows for the exacerbations/relapses with a high risk-window of 1-42 days post-exposure for IBD exacerbations and 1-60 days for MS relapses (Table A3).

As per the protocol, a decision on whether or not the THIN identification process for exacerbations and relapses should be run across all study seasons was made with the Adjudication Committee based on the PPV, NPV and sensitivity results of the validation of the THIN identification against the questionnaire (9.10 Quality Control).

### 9.4.3 Other Variables

Details of age at vaccination, sex, and chronic diseases were obtained from the THIN database. Chronic diseases were those conditions with which an influenza vaccination was recommended for people under the age of 65 years, namely chronic respiratory, heart, kidney, liver or neurological disease, immunosuppression or diabetes.

Co-administration of other vaccines may occur as is consistent with clinical practice. In particular, pneumococcal polysaccharide vaccine may be given concurrently. Administration of pneumococcal polysaccharide vaccination within 28 days of cTIV was identified from vaccination records.

## 9.5 Data Sources and Measurement

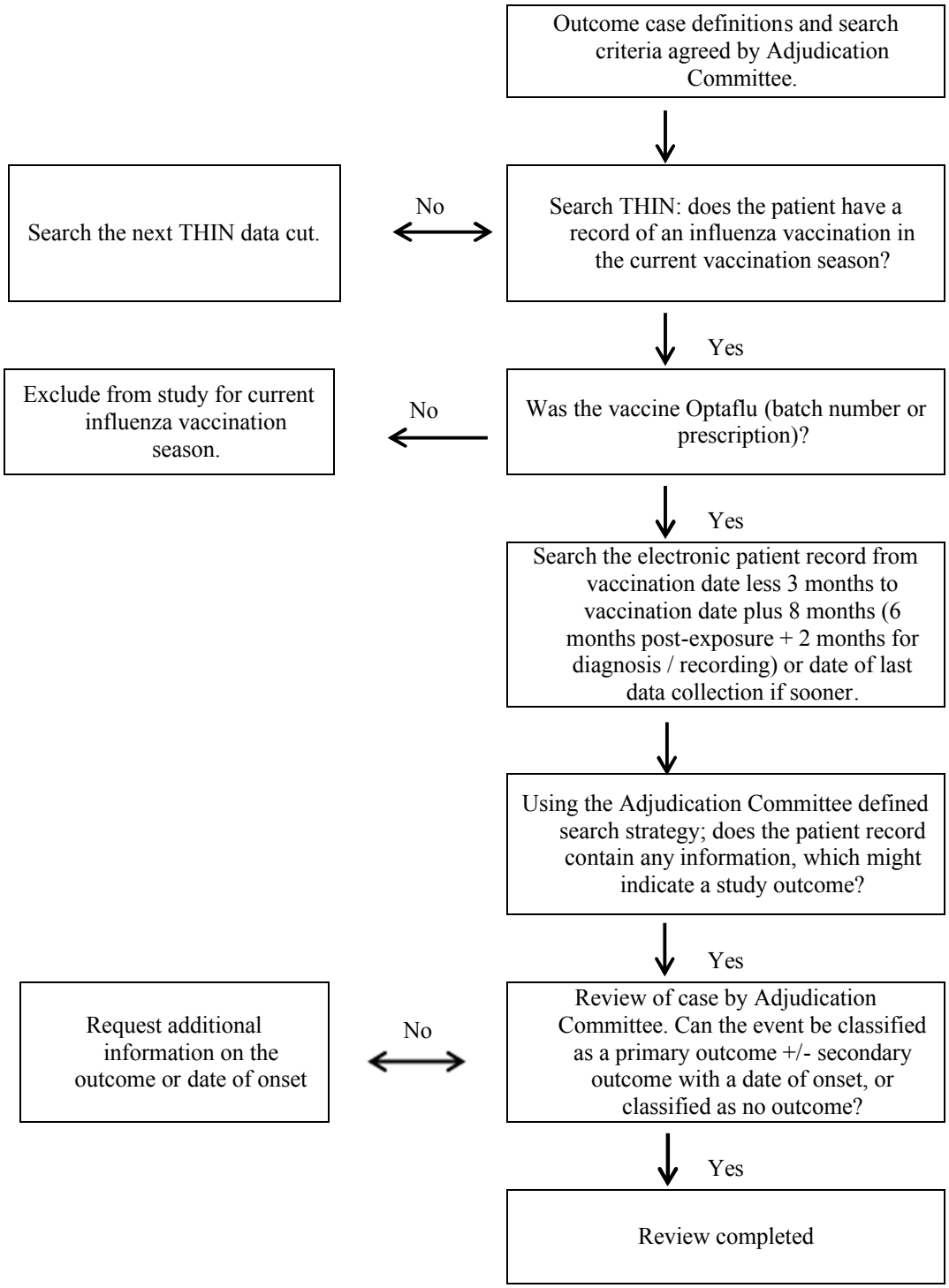
Information on all variables was obtained from THIN data. THIN and other UK electronic primary care record databases had previously been used for the study of seizures (Gasse et al. 2000; Gao et al. 2008), GBS (Tam et al. 2007; Stowe et al. 2009), Bell's palsy (Rowlands et al. 2002; Stowe et al. 2006) demyelinating disease and optic neuritis (Gupta et al. 2005), anaphylaxis (Andrews et al. 2010), vasculitis (Watts et al. 2009), thrombocytopenia (Schoonen et al. 2009) and IBD (Lewis et al. 2002; Gupta et al. 2005). No studies of relapses of MS or exacerbations of IBD using primary care data were identified from the literature when these outcomes were added to the protocol so they were validated against a practice questionnaire (9.10 Quality Control).

The overall procedures for the case ascertainment and review are shown in Figure 1.



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**Figure 1: Identification of study outcomes**






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### 9.5.1 Exposure of interest

Exposure was defined as a record of influenza vaccination on THIN, dated in one of the study vaccination seasons, which had a cTIV batch number or specifically named cTIV as the vaccination given. The unique batch numbers for cTIV available commercially in areas covered by THIN (the whole of the UK) were provided by the market authorization holder. THIN includes a copy of the primary record of vaccination. Records, which include 'refused' or 'advise given', were excluded. Patients who received cTIV in more than one study vaccination season were included for each exposure provided that there was no overlap in the observation period. Had there been overlap (due to a late vaccination one season and a very early one the next) the second vaccination would have been excluded. In practice, there were no overlapping observation period.

### 9.5.2 Operational Outcome Definition and Identification Process

Figure 1 shows the identification process for incident outcomes. For each outcome, possible occurrences were identified by searching the THIN records (the Medical, Additional Health Data files and, for some outcomes, the therapy file) for specific Read and drug codes, and for key terms in the unstructured text linked to the codes (see 9.3.1 Source population). The codes and key terms included in the searches are listed in Annex 2 Table A4 by outcome. The period of observation for each exposed person was from three months before the date of vaccination until six months afterwards. However, patient records were searched to eight months after exposure to allow time for diagnosis and communication of the diagnosis from secondary to primary care.

The Adjudication Committee reviewed each possible incident outcome that was identified. The use of text terms resulted in identification of a range of events including negatives (for example 'no symptoms of anaphylaxis' or 'no known allergy to penicillin'). Review of potential events therefore involved deciding if an event had actually occurred, as well as comparing any possible outcome to the primary and study case definitions to decide if the event fulfilled these definitions. The Read code and any linked unstructured text (regardless of which was initially identified) along with the remaining coded medical record were compared to the case definitions for that outcome. When there was sufficient information, the event was categorized as no outcome, an outcome against the primary case definition or an outcome against both case definitions. A date of onset was assigned for all outcomes from information in the patient record as described in the case definition.

Additional data was requested from the practice via a third party if there was insufficient information to complete the review. This additional data could include additional unstructured text, an updated record, correspondence with secondary care and death certificates. The event was reviewed again with returned additional information. Each event was reviewed by at least two members of the Adjudication Committee. When there



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was disagreement in the conclusion of the review, then the data and decisions were discussed. In the event that agreement still had not been reached, then the final decision would have been made by the person with the most relevant clinical background, either the neurologist (seizures, Bell's palsy, neuritis (optic and brachial), paraesthesia, demyelination and non-infectious encephalitis) or the immunologist (severe allergic reactions, thrombocytopenia, vasculitis, IBD).

When more than one code or text term was identified in a patient record then each was reviewed to ascertain if a second event had occurred. Deaths were reviewed by the Adjudication Committee for evidence of an outcome. All text was depersonalized before review. Depersonalization was initially completed electronically and then by double review. The questionnaire validation of the identification of IBD exacerbations and MS relapses is described in Section 9.10.

The Adjudication Committee review was blinded to the date of vaccination for case definition and risk window development, and for all outcome and questionnaire reviews. The Adjudication Committee neurologist reviewed each possible neurological outcome while the immunologist reviewed all possible allergic, autoimmune and hematological outcomes.

Some conditions could potentially fit within more than one outcome. For example, ADEM could be included within demyelination or non-infectious encephalitis categories. Had this occurred, then cases would only be counted within one outcome except for GBS, which could be studied alone, and in the general demyelinating disease group.

### 9.5.3 Other variables

Details of age at vaccination, sex, chronic diseases and pneumococcal polysaccharide vaccination were also obtained from the THIN data. Chronic diseases dated before vaccination were identified using Read codes published for influenza vaccine uptake monitoring purposes by primary care practices in the UK (Primis 2013).

## 9.6 Bias

It is possible that differential misclassification will occur in cases diagnosed immediately after vaccination if it is known that a study outcome has been associated with vaccinations in the past, for example in GBS. The sensitivity analyses using the study case definitions developed as part of this study should reduce this bias, since the study case definitions are stricter. However, while these adjudications will be more specific, these analyses will have fewer cases available. Other biases and confounders, such as selection bias, were reduced, as only people exposed to cTIV were included in this analysis rather than an external comparator.



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Thrombocytopenia after recent chemotherapy or radiotherapy was an exclusion criterion in both case definitions for this outcome because of potential confounding. It is well documented that these treatments increase the risk of thrombocytopenia. They are also likely to decrease the chance of vaccination during therapy due to both clinical and social factors.

The review of possible outcomes by the Adjudication Committee was blinded to date of cTIV exposure. Blinding was maintained during a study season by removing details of exposure from all medical records transferred to the Adjudication Committee to review and transferring only these records. To allow retrospective review of a possible outcome after an end of season interim report (for example additional data was obtained), the patient records remained blinded and only one Committee member could have had access to the analysis data. The remaining two Committee members completed the review. However, there may have been some limits to the blinding. The Adjudication Committee was aware this study concerned a seasonal vaccine. Since the majority of influenza vaccinations are given during early Autumn the Committee may have assumed an approximate date of exposure. In practice exposures between September and March were included and the vaccine was not distributed in the UK until November in the second season, which may have reduced the potential bias due to the assumptions around the exposure date to some extent..

### 9.7 Study Size

As this study was completed on the THIN database, the number of subjects available for inclusion was fixed and only the time period for the study could vary.

The total sample size of 9000 subjects planned to rule out outcomes occurring with a frequency of 1 in 3000 if no outcome is observed (Eypasch et al. 1995). Table 2 shows the number of expected outcomes based on incidence rates and risk windows prior to the study. For most outcomes this will be zero and so a risk of 1 in 3000 can be ruled out. The exceptions are Bell's palsy and convulsions (when the longer risk window is used). Using the published background rates as the expected and 95% power, 9000 exposed will rule out a rate ratio of 50 for Bell's palsy and 39 for convulsions (Rothman et al. 1998). At 90% power and 9000 exposed, the rate ratio that can be ruled out will be 30 for Bell's palsy and 24 for convulsions. It should be noted that the background rates were from the general population (mostly over 10 years of age). Those who receive seasonal influenza vaccinations are likely to be at higher risk of outcomes.

Table 3 reports the estimated number of exposed patients available for study using sales estimates provided by NVD, a lower sales figure (50% of that suggested) and the THIN coverage. The estimate assumed that 94% will have a batch number identified based on a feasibility study. It also assumed that an additional one third of doses would not be



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identified because of uneven geographic distribution of use, some occupational health vaccination of key workers, errors in batch numbers and unused doses.



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**Table 2: The expected number of outcomes estimated prior to the study and based on a sample size of 9000[1]**

| | Background annual incidence (per 100,000) | Post-exposure risk window (days) | Pre-exposure low risk window (days) | Expected number of outcomes outside risk windows | Expected number of outcomes in high risk window |
|---|---|---|---|---|---|
| Anaphylactic reaction / angioedema | 8.4 | 2 | 14 | 1 | 0 |
| Bell's palsy | 20.2 | 90 | 60 | 1 | 1 |
| Convulsions | 44 | 8 | 14 | 3 | 0 |
| Convulsions[2] | 44 | 23 | 14 | 3 | 1 |
| First central nervous system demyelinating event | 15.9 | 61 | 90 | 0 | 0 |
| GBS alone | 1.5 | 61 | 90 | 0 | 0 |
| Paraesthesia (serious events) | Assume 9.0 | 35 | 35 | 0 | 0 |
| Neuritis, (optic and brachial) | 7.0 | 42 | 30 | 0 | 0 |
| Optic neuritis | 4.4 | 42 | 30 | 0 | 0 |
| Brachial neuritis | 3.0 | 42 | 30 | 0 | 0 |
| Non-infectious encephalitis | 4.3 | 60 | 14 | 0 | 0 |
| Vasculitis | 2.0 | 30 | 90 | 0 | 0 |
| Inflammatory bowel disease | 7.6 | 61 | 90 | 0 | 0 |
| Thrombocytopenia | 3.9 | 43 | 30 | 0 | 0 |

GBS Guillain-Barré Syndrome

[1]Expected based on 9000 exposed.

[2]More than one possibility with different time windows.



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**Table 3: The number of cTIV exposed patients in THIN by influenza vaccination season estimated prior to the study**

| Season | Sales estimate[1] | | % Population covered[2] | Maximum exposed | | 94% with batch number | | Assume ⅔ identified[3] | |
|---|---|---|---|---|---|---|---|---|---|
| | Lower | Upper | | Lower | Upper | Lower | Upper | Lower | Upper |
| **2012/13** | 5250 | 5650 | 11% | 578 | 622 | 543 | 541 | 362 | 389 |
| **2013/14[1]** | 303,000 | 505,000 | 6% | 18,180 | 30,300 | 17,089 | 28,482 | 11,393 | 18,988 |
| **Total** | | | | | | | | 11,755 | 19,377 |

[1] For 2013/2014, the higher figure is the market authorization holder estimate, the lower figure is 60% of this figure.
[2] For 2012/13 most use was expected to be in Scotland with 11% THIN coverage, 2013/14 use was expected throughout the UK with 6% THIN coverage. [3]Assuming loss due to uneven distribution, occupational vaccination, incorrect batch numbers etc.

## 9.8 Data transformation

All variables were identified from the THIN database – see section 9.4 for details. The extraction of data was completed by staff at Cegedim CSD following a programming specification developed with the Principal Investigator. IMS Health acquired CSD in season 3 and continued the data extraction.

The extraction was completed at each collection of practice data from the beginning of an influenza vaccine season until eight months after the date of the last cTIV vaccination in that season (six months observation plus two months for diagnosis and recording) – see Figure 1. The record of the seasonal influenza vaccination was removed before data on possible outcomes were sent to the Principal Investigator and the Adjudication Committee for review.

## 9.9 Statistical methods

The study was intended as a hypotheses generating study.

### 9.9.1 Main summary measures

- The observed to expected ratio of outcomes based on time from cTIV exposure is reported and the time from exposure plotted.
- Incidence rates after exposure are reported.
- Age is described as mean and standard deviation.



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- Sex, history of each of the chronic conditions and pneumococcal polysaccharide vaccine are reported as a number and a percentage of the total.

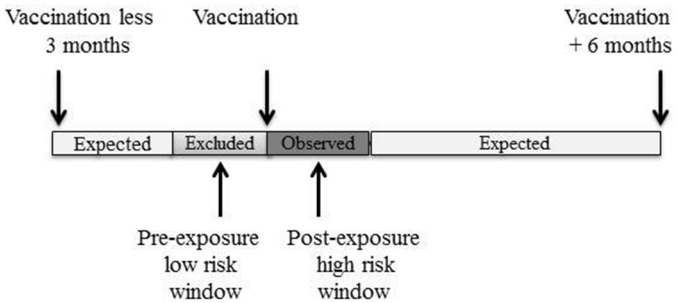
### 9.9.2 Main statistical methods

**Outcomes pre-and post- cTIV vaccination**

Within each study outcome, for each case, which occurred during the observation period (3 months prior to 6 months post exposure), the number of days between the date of onset of the outcome (assigned by the Adjudication Committee) and exposure was calculated. A plot was produced to show the temporal distribution of study outcomes in relation to the vaccination date and the high risk-window.

When an outcome had occurred in the high risk-window the ratio of the rates of observed to expected cases was calculated to investigate whether a signal of an association between cTIV exposure and a study outcome had been generated. This was only possible when an outcome was found in both the observed and expected period. The observed rate was the total number of occurrences of that outcome in the high risk-window divided by the total number of person time (in days) of observation in that high risk-window. The expected rate was the total number of occurrences of that outcome divided by the total number of person time (in days) of observation in the period outside both the high risk-window and the low risk pre-exposure window (Figure 2). In outcomes where there was a delay between exposure and the start of the high risk-window this time was also excluded from the expected time. Observation could be right censored if the observation stopped because the patient left the practice or the practice stopped supplying data to THIN. The 95% confidence intervals were estimated to show if the ratio was statistically significantly different to one.

**Figure 2**: **Expected and observed time periods for the analysis**






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**Outcome incidence**

The incidence of each study outcome in the six months after exposure to cTIV was estimated. The numerator was the number of outcomes adjudicated to have a date of onset within these six months and the denominator was the total period of observation from the date of exposure to the earliest of the following dates: exposure plus six months, or the date of the last data collection from that practice, death or deregistration from the practice, or an incident outcome.

### 9.9.3 Missing values

All eligible exposed patients were included regardless of whether or not their electronic practice record continued to six months post-vaccination (Figure 1). There were no missing values for age and sex which is recorded in >99% of THIN patients. Concomitant diseases were included if noted in the coded electronic patient record and were assumed to be absent if not noted.

### 9.9.4 Sensitivity analyses

A sensitivity analyses of incident outcomes repeated the estimate of incidence of each outcome in the six months after cTIV exposure using the study case definition described in Section 9.4.2. This analysis was completed to minimize bias from differential misclassification.

A subgroup analysis used the primary case definition but included only people in those chronic disease groups who are recommended to have influenza vaccinations, namely those with diabetes, immunosuppression or chronic respiratory, heart, liver, or neurological disease.

Two sensitivity analyses were completed for the IBD exacerbation and MS relapse validation. The first included people prescribed doses of steroids which were lower than the recommended dose but which might be used by a primary care physician. This analysis was planned before the data cut from THIN. See Annex 2 Table A2 for details. The second sensitivity analysis was completed after the data were reviewed in an effort to suggest ways to improve the performance of the algorithm. This analysis excluded IBD exacerbations identified by a new episode of 5-aminosalicylic acid treatment.

### 9.9.5 Amendments to the statistical analysis plan

The addition of combined years analysis was added to the Statistical Analysis Plan in season 2 with updates to plot tables and clarification of exclusion of expected time in



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outcomes where there was a delay between exposure and the start of the high risk-window, and updated reformatting. In season 3 the identification and validation of IBD exacerbations and MS relapses and the decision not to run this analysis was added. Also the plan was reformatted in line with IMS procedures. File names were updated at each season. A second sensitivity was added to the validation of the algorithm to identify IBD exacerbations in an effort to improved its performance. This second analysis excluded IBD exacerbations identified by a new episode of 5-amonisalicylic acid treatment.

## 9.10 Quality Control

The data cuts were subject to routine quality assurance following standard operative procedures at CSD and later IMS Health.

**Exposure validation**

A pre-study feasibility assessment investigated the recording of seasonal influenza immunization on the THIN database and the identification of brand used (Hall et al. 2013). In the 2010-2011 and 2011-2012 influenza vaccination seasons the percentage of people over 65 years of age with a record of an influenza immunization on THIN was slightly higher than those published regional statistics. A brand name or batch number could be identified for 94.3% of a sample of 1,000 immunizations.

**Incident outcome validation**

All possible incident outcomes identified on THIN were reviewed by the Adjudication Committee and categorized as an outcome or not with a date of onset assigned for outcomes. The procedure for adjudication is explained in detail in Section 9.5.2.

**Exacerbation and relapse algorithm validation**

No studies of relapse and exacerbation of MS or IBD using electronic primary healthcare data were identified from the literature when these outcomes were added to the protocol. Consequently, the case identification for each one (Section 9.4.2) was validated against practice questionnaires before any other analysis was performed. The questionnaire, which was developed with the Adjudication Committee, gave a case definition for exacerbations or relapses, and requested details of any of these events in the patient record dated during observation for that patient (Annex 3 Figure A1). Questionnaires were sent for patients with a record of prevalent disease who were registered at practices that consider participation in questionnaire studies. The questionnaires were sent to the practice after the end of the observation period for that patient. cTIV exposure was not mentioned in the questionnaire or the covering letter. The Adjudication Committee also reviewed each returned questionnaire for exacerbations and the date. The review was blinded to date of exposure.



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The exacerbation / relapses reported on the questionnaires were compared to those identified by the THIN based algorithm to estimate the PPV, NPV and sensitivity and 95% confidence intervals (CI) by patient and by episode. A patient could have more than one exacerbation or relapse. An additional exacerbation / relapse was defined by the Adjudication Committee as a new outcome after a gap of at least 30 days.

The sample size estimate for the validation of IBD exacerbations was 50 completed questionnaires. This was based on the assumption of 5000 exposed to cTIV in the third season (the number required after season 2 and Table 3) and a prevalence of 2% (initial estimate from those exposed to cTIV in 2012 – 2013 in THIN), and so 100 prevalent cases. If half of these patients had an IBD exacerbation and 80% are categorized correctly from THIN data then this would provide a PPV of 0.8 (0.59, 0.93). For relapse of MS a practice questionnaire was sent to all patients with prevalent MS exposed to cTIV in the third season since no cases of prevalent MS were identified among the 623 exposed to cTIV in the first season of study.

### 9.11 Other Aspects

None.

### 9.12 Protocol deviations

None.

## 10. RESULTS

### 10.1 Participants

This analysis reports the results of three influenza seasons (2012-2013, 2013-2014 and 2014-2015). A total of 4578 of the planned 9000 exposures were identified.

The THIN database search identified 4900 exposures to cTIV and 4578 were included in the analysis after exclusions: 81 people were under 18 years of age, 244 had registered with the practice within the previous 12 months and 2 people had been immunized after they had transferred out of the practice.

### 10.2 Descriptive data

The mean age of the population at exposure was 60.5 years (SD 16.5), 42.6% were male and 56.9% had a history of one or more chronic illness with which influenza vaccination is recommended (Table 4). The most frequent chronic diseases found are given in Table 5. The mean period of observation including pre- and post- exposure time was 272 days (SD 15.2). In 4.6% of the exposed population a pneumococcal polysaccharide vaccine was given within 28 days of cTIV.



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**Table 4: Baseline characteristics of the exposed cohort at cTIV vaccination**

| | Total (%) | Male (%) | Female (%) |
|---|---|---|---|
| Total number | 4,578 | 1,950 (42.6%) | 2,628 (57.4%) |
| Days observation, mean (SD) | 271.9 (15.2) | 272.2 (13.7) | 271.7 (16.2) |
| Age, years | | | |
| mean (SD) | 60.5 (16.5) | 61.3 (14.9) | 59.9 (17.6) |
| 18 - 29 | 268 (5.9) | 73 (3.7) | 195 (7.4) |
| 30 - 44 | 539 (11.8) | 199 (10.2) | 340 (12.9) |
| 45 – 59 | 1,054 (23.0) | 483 (24.8) | 571 (21.7) |
| 60 – 74 | 1,841 (40.2) | 859 (44.1) | 982 (37.4) |
| >75 | 876 (19.1) | 336 (17.2) | 540 (20.6) |
| With any chronic disease | 2605 (56.9) | 1255 (64.4) | 1350 (51.4) |
| Pneumococcal Polysaccharide vaccination* | 209 (4.6) | 96 (4.9) | 113 (4.3) |

*+/-28 days of cTIV exposure

**Table 5: Chronic diseases in cTIV exposed subjects**

| Condition | Number (%) |
|---|---|
| Diabetes | 858 (18.7) |
| Heart disease | 791 (17.3) |
| Asthma* | 561 (12.3) |
| Kidney disease† | 474 (10.4) |
| Neurological system disease§ | 429 (9.4) |
| Other respiratory disease | 405 (8.9) |
| Immunosuppression‡ | 164 (3.6) |
| Liver disease | 61 (1.3) |

*Inhaled / oral steroid prescription or hospitalized in the last year.
§Including stroke / TIA, cerebral palsy and multiple sclerosis.
†Latest chronic kidney disease stage recorded is 3-5.
‡Diagnosis or treatment.

## 10.3 Outcome Data

### Case adjudication

The searches of THIN identified 1011 events, which were reviewed by the Adjudication Committee as possible outcomes. The committee categorized 21 of these events as



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incident study outcomes against the primary case definition and assigned a date of onset while blinded to the exposure date for that person. Five incident outcomes were excluded at the analysis stage because they had a date of onset outside the observation period (see 10.6 Adverse Reactions and Events).

The Adjudication Committee therefore identified a total of sixteen incident outcomes with a date of onset within the observation period based on a primary case definition: five thrombocytopenia, four convulsions, two each of paraesthesia and vasculitis, and one each of severe allergic reaction, Bell's palsy and IBD. Eleven out of sixteen incident outcomes fulfilled the stricter study case definition, four thrombocytopenia, two each of paraesthesia and vasculitis, and one each of convulsions, severe allergic reactions and IBD. No episodes of neuritis, encephalitis or first central nervous system demyelinating event were identified in the study period. There were 50 deaths in the study period. No evidence of an outcome was identified in any death. No person had more than one study outcome confirmed by the Adjudication Committee and no person had more than one incident episode of the same outcome either.

## 10.4 Main Results

### Outcomes pre-and post- cTIV vaccination

Three of the sixteen outcomes with a date of onset within an observation period were dated in a high risk-window, one each for convulsions, thrombocytopenia and IBD (Table 6). The remaining thirteen outcomes occurred outside the high risk-window for that outcome. Plots of time from cTIV exposure to date of onset of an outcome using the primary case definition are given in Annex 3 (Figures B1 to B7). The plots for those outcomes with a date of onset in a high risk-window are repeated below.

**Table 6: The number of outcomes and days observation in observed and expected time periods and ratio of observed to expected by outcome**

| Outcome* | Total | Observed* number of outcomes (days observation) | Expected§ number of outcomes (days observation) | Observed to expected (95% CI) |
|---|---|---|---|---|
| Total all outcomes | 16 | - | - | - |
| Severe allergic reaction | 1 | 0 (9,156) | 1 (1,171,404) | - |
| Bell's palsy | 1 | 0 (410,065) | 1 (555,329) | - |
| Convulsions† | 4 | | | |
| (using day 0-7 high risk-window) | | 0 (36,623) | 4 (1,143,937) | - |
| (using day 8-30 high risk-window) | | 1 (105,142) | 3 (1,038,795) | 3.3 (0.3, 31.7) |
| First CNS demyelinating event‡ | 0 | 0 (278,489) | 0 (554,143) | - |



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| | | | | |
|---|---|---|---|---|
| GBS[†] | 0 | | | |
| (using day 7-60 high risk-window) | | 0 (246,443) | 0 (554,143) | - |
| (using day 1-60 high risk-window) | | 0 (273,911) | 0 (554,143) | - |
| Paraesthesia[†] | 2 | | | |
| (using day 7-42 high risk-window) | | 0 (164,486) | 2 (984,028) | - |
| (using day 43-77 high risk-window) | | 0 (159,172) | 2 (824,856) | - |
| Non-infectious encephalitis | 0 | 0 (273,911) | 0 (902,071) | - |
| Neuritis (optic and brachial) | 0 | 0 (191,954) | 0 (910,780) | - |
| Vasculitis | 2 | 0 (137,187) | 2 (690,867) | - |
| Inflammatory bowel disease | 1 | 1 (196,532) | 0 (910,780) | - |
| Thrombocytopenia | 5[∞] | 1 (196,532) | 3 (910,780) | 1.5 (0.2, 14.9) |

GBS: Guillain-Barré syndrome.

[*]Observed incident outcomes occurring in the high risk-window.

[§]Incident outcomes occurring in the expected time (background rate outside the high- and pre-exposure low risk-windows, defined in Table 1, and excluded time).

†all outcomes are included in both high risk-window analyses but the distribution between observed and expected columns might vary.

[‡]Includes GBS.

[∞]One episode is in the low risk period and therefore not included in the observed to expected calculation. See Figure B4.

Of the three outcomes in the high risk-window, one convulsion was during the later high risk-window for that outcome, 8 – 30 days after cTIV (Figure 3) with an observed to expected ratio of 3.3 (0.3, 31.7) (Table 6). One incident thrombocytopenia was in the high risk-window, another had a date of onset in the low risk-window, and three were in the expected period (Figure 4). The observed to expected ratio for thrombocytopenia was 1.5 (95%CI 0.2, 14.9). The plot for IBD is given in Figure 5. No observed to expected estimates were computed, as there was no IBD outcome outside the high risk-window. Results using the study case definitions are reported in Section 9.9.4.



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**Figure 3: Distribution of convulsions by time from cTIV exposure**

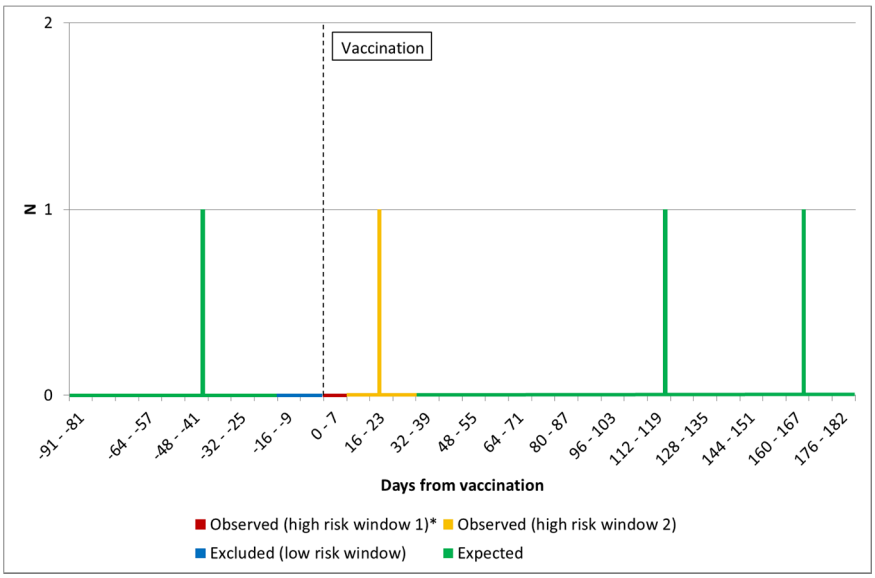



Figure uses the primary case definition. For explanation of the observed, excluded and expected time periods see Section 9.9.2 including Figure 2, and for details of the plots see Annex 3.

**Figure 4: Distribution of thrombocytopenia by time from cTIV exposure**

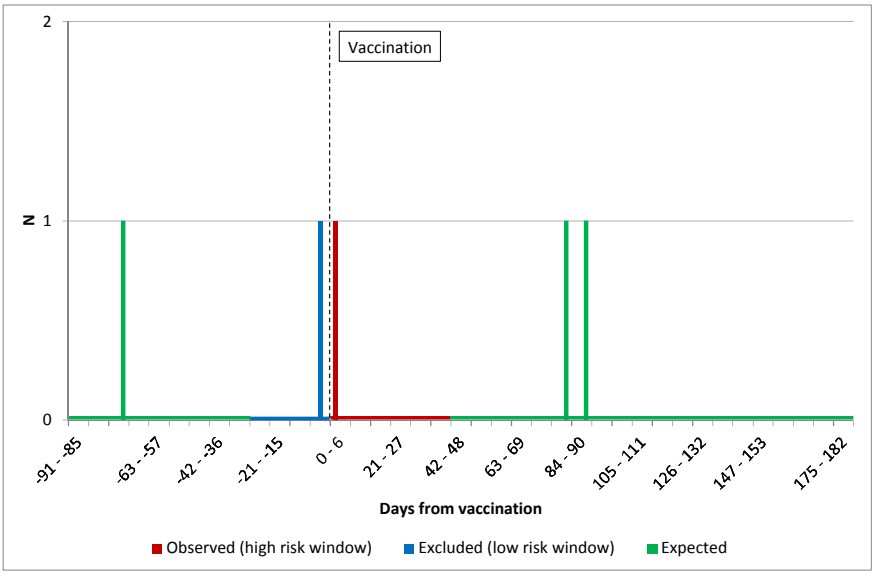



Figure uses the primary case definition. For explanation of the observed, excluded and expected time periods see Section 9.9.2 including Figure 2, and for details of the plots see Annex 3.



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**Figure 5: Distribution of IBD onset by time from cTIV exposure**

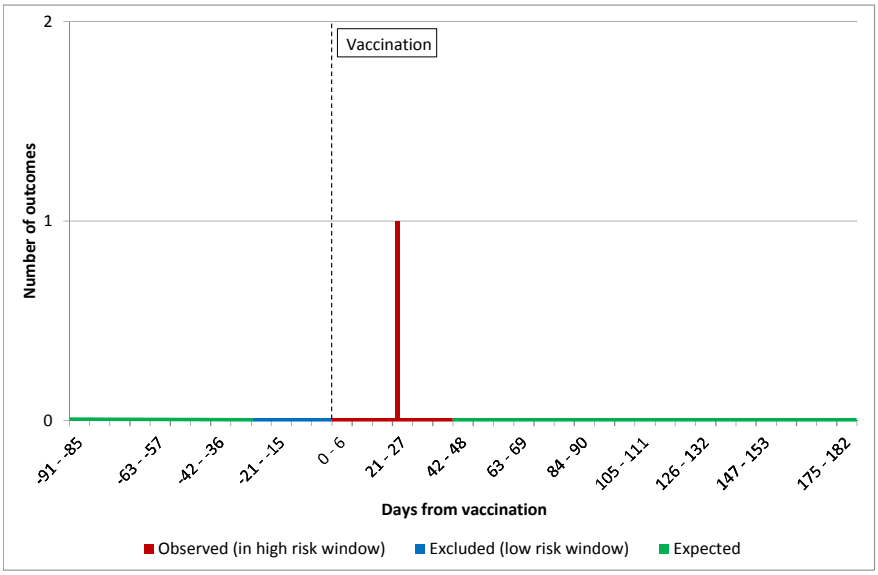



Figure uses the primary case definition. For explanation of the observed, excluded and expected time periods see Section 9.9.2 Statistical Methods including Figure 2, and for details of the plots see Annex 3.

## Outcome incidence after exposure

Eleven out of the sixteen incident outcomes using the primary case definition occurred in the six month post-cTIV exposure. The incidence of these outcomes is reported in Table 7 for the total population.



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**Table 7: Incidence per 100,000 person years in the six months after cTIV vaccination**

| Outcome* | Number of incident outcomes* | Incidence per 100,000 person years (95% CI)[§] |
|---|---|---|
| Severe allergic reaction | 1 | 44.1 (6.2, 313.1) |
| Bell's palsy | 1 | 44.1 (6.2, 313.1) |
| Convulsions | 3 | 132.4 (42.7, 410.4) |
| First CNS demyelinating event[†] | 0 | - |
| GBS | 0 | - |
| Paraesthesia[‡] | 0 | - |
| Non-infectious encephalitis | 0 | - |
| Neuritis (optic and brachial) | 0 | - |
| Vasculitis | 2 | 88.2 (22.1, 352.8) |
| Inflammatory bowel disease | 1 | 44.1 (6.2, 313.2) |
| Thrombocytopenia[‡] | 3 | 132.3 (42.7, 410.3) |

GBS: Guillain-Barré syndrome. CNS: central nervous system

*Using the primary case definition.

[§]Total observation = 2266 years for convulsions; otherwise 2267 years.

[†]Includes GBS.

[‡]Cases of paraesthesia, convulsions and thrombocytopenia before cTIV exposure are not included.

## 10.5 Other Analysis

Eleven of the sixteen incident outcomes identified by the Adjudication Committee also fulfilled the study case definition. These included four thrombocytopenia, two each of paraesthesia and vasculitis, and one each of IBD, convulsions and serious allergic reaction. Only the IBD was found in the high risk-window. No observed to expected analysis could be conducted, as there was no incident IBD was identified outside the high risk-window. The incidence of outcomes matching the study case definition in the six months after cTIV exposure is given in Table 8.

Six of the sixteen incident outcomes using the primary case definition were in people identified as having a history of chronic disease. Table 9 reports the incidence of the outcomes in this sub-category.



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**Table 8: Outcome incidence per 100,000 person years in the six months after cTIV vaccination: study case definition outcomes in all exposed**

| Outcome | Using study case definition | |
|---|---|---|
| | Number of outcomes* | Incidence (95% CI) † |
| Severe allergic reaction | 1 | 44.1 (6.2, 313.1) |
| Bell's palsy | 0 | - |
| Convulsions | 0 | - |
| First CNS demyelinating event‡ | 0 | - |
| GBS | 0 | - |
| Paraesthesia | 0 | - |
| Non-infectious encephalitis | 0 | - |
| Neuritis (optic and brachial) | 0 | - |
| Vasculitis | 2 | 88.2 (22.1, 352.8) |
| Inflammatory bowel disease | 1 | 44.1 (6.2, 313.2) |
| Thrombocytopenia | 2 | 88.2 (22.1, 352.7) |

GBS: Guillain-Barré syndrome.

*Study case definition.

†total observation time for all outcomes 2267 using the study case definition

‡Includes GBS.



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**Table 9: Outcome incidence per 100,000 person years in the six months after cTIV vaccination: primary case definition outcomes in the subset of people with chronic disease**

| | Chronic disease only | |
|---|---|---|
| **Outcome** | **Number of outcomes[§]** | **Incidence (95% CI) [†]** |
| Severe allergic reaction | 0 | - |
| Bell's palsy | 1 | 77.6 (10.9, 551.0) |
| Convulsions | 2 | 155.3 (38.8, 620.9) |
| First CNS demyelinating event[‡] | 0 | - |
| GBS | 0 | - |
| Paraesthesia | 0 | - |
| Non-infectious encephalitis | 0 | - |
| Neuritis (optic and brachial) | 0 | - |
| Vasculitis | 0 | - |
| Inflammatory bowel disease | 0 | - |
| Thrombocytopenia | 3 | 232.8 (75.1, 722.0) |

GBS: Guillain-Barré syndrome.
[§]primary case definition.
[†]total observation time for all outcomes 1288 years for chronic disease using the primary definition.
[‡]Includes GBS.



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**IBD Exacerbation and MS relapse algorithm validation**

In the third season 49 (2.7%) people with a history of IBD and 18 (1.0%) with MS were identified from the overall cohort of 1849 cTIV exposed (Table 9). Questionnaires were sent to participating practices for 44 patients with IBD and 15 with MS. Thirty (61.2%) completed questionnaires were received for the IBD patients and 13 (72.2%) for MS patients. Uncompleted questionnaires were returned for 1 patient who did not have prevalent IBD and 1 MS patient who had left the practice.

In the 30 people with prevalent IBD and a completed questionnaire, 10 exacerbations were identified from THIN through the algorithm but only 3 were reported on the questionnaire with a date of onset within the observation period. An additional exacerbation was reported but was excluded as the date of onset was outside that patient's observation period (over 7 months prior to exposure). The PPV for IBD exacerbations identified from THIN was 0.10 (95%CI 0.01, 0.46) in the main analysis (Table 10). The sensitivity analysis that included any or unknown doses of oral steroid treatments in the algorithm had a PPV for episodes of 0.08 (0.004, 0.40). It was noted that a number of false positive exacerbations had been identified by a prescription of a 5-aminosalicylic acid at least 112 days after the previous prescription. A second post-hoc sensitivity analysis was done to exclude these exacerbations. In that analysis, the PPV was 0.25 (95% CI 0.01, 0.78) (NPV 0.92 (0.73, 0.99); sensitivity 0.33 (0.02, 0.87)).



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**Table 10: Validation of the algorithm for identification of IBD exacerbation and MS relapses**

| | IBD exacerbations | MS relapses |
|---|---|---|
| Prevalent cases(n) | 49 | 18 |
| Questionnaires: | | |
| sent (n, % of prevalent cases) | 44 (89.8) | 15 (83.3) |
| returned and suitable (n, % of prevalent cases) | 30 (61.2) | 13 (72.2) |
| exacerbations / relapses (n) | 3 | 2 |
| people with an exacerbation /relapse (n)* | 3 | 2 |
| THIN algorithm in people with a questionnaire: | | |
| sub-group with a returned and suitable questionnaire (n) | 30 | 13 |
| exacerbations / relapses (n)† | 10 | 1 |
| people with an exacerbation /relapse (n)*† | 9 | 1 |
| Exacerbations/relapse‡: | | |
| PPV (95%CI) | 0.10 (0.01, 0.46) | - |
| NPV (95%CI) | 0.91 (0.70, 0.98) | - |
| Sensitivity (95%CI) | 0.33 (0.02, 0.87) | - |
| People with an exacerbation/relapse | | |
| PPV (95%CI) | 0.33 (0.09, 0.69) | - |
| NPV (95%CI) | 1 (0.81, 1) | - |
| Sensitivity (95%CI) | 1 (0.31, 1) | - |

*multiple exacerbations/relapses can happen during the observation period in one person with prevalent IBD or MS

†exacerbations/relapses identified from the questionnaire and those identified on THIN are not necessarily the same events.

‡considered as different episodes if the date of onset in the questionnaire is equal or more than 30 days apart from the date of diagnosis derived from the THIN data.

No PPV was estimated for MS relapses as only two episodes were identified from the questionnaires. This number is too small to give a clear picture on the performance of the database algorithm in identifying MS relapses. However, neither of the two relapses reported on the questionnaire were identified from THIN, while one episode was falsely identified. The findings provided no clear indication of how the MS algorithm could be improved.



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It was concluded with the Adjudication Committee that the case definitions and resultant algorithm were not sufficiently accurate and reliable to use across the study population. There was no indication as to how the algorithms could be further improved. The Adjudication Committee had defined high risk-windows of 1-42 days for IBD exacerbations and 1-60 days for MS relapses before analysis of the questionnaires and THIN data. All exacerbations and relapses noted on the questionnaire were dated after these windows (days 171, 175 and 180 for IBD exacerbations, and days 114 and 131 for MS relapses).

### 10.6 Adverse Reactions and Events

The data included in the study were always secondary data either from THIN database or from practice questionnaires requesting details from a record review.

In this study no occurrence or patterns for adverse events other than the outcomes of interest were actively sought.

The study identified episodes of a pre-defined list of outcomes of interest. All episodes identified for the outcomes of interest occurring in the observation period (3 months pre- to 6 months post-vaccination) were included in the analysis without an assessment of the relatedness to the vaccine and are summarized in Table 6.

In addition to the outcomes reported in Table 6, additional incident events of the outcomes that were identified during the course of the study, but were not included in the analysis are discussed here. The Adjudication Committee categorized five events as outcomes but assigned a date of onset that was outside the observation period for that individual. These outcomes included 1 thrombocytopenia, 1 severe allergic reaction, 2 vasculitis and 1 IBD. The IBD had a date of onset 238 days before cTIV exposure. The other outcomes had dates of onset during the period between six and eight months after exposure, which was included in the THIN searches to allow capture of events with delayed diagnosis or reporting to the practice (See 9.4.2 Outcomes). The outcomes that occurred more than six months after exposure were thrombocytopenia (192 days after exposure), severe allergic reaction (186 days after exposure) and vasculitis (197 and 240 days after exposure).

## 11. DISCUSSION

### 11.1 Key results

A total of 4578 cTIV exposures were included in this study over three seasons between 2012 and 2015.



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No first demyelinating events (including GBS), non-infectious encephalitis, or neuritis (optic and brachial) were observed over the full observation period pre- and post-vaccination. No severe allergic reaction, Bell's palsy, paraesthesia, or vasculitis were identified in the high risk-window when an outcome with potential causal association with cTIV exposure might be expected to occur. For the remaining three outcomes (thrombocytopenia, convulsions and IBD), one incident episode of each was identified with a date of onset during the high risk-window. The convulsion was in the later high risk-window for this outcome which included days 8 to 30 after exposure. The ratio of observed to expected was 1.5 (95% CI 0.2, 14.9) for thrombocytopenia and 3.3 (95% CI 0.3, 31.7) for convulsions. Since the incident IBD identified was in the high risk-window and no IBD was identified in the expected window, no observed to expected could be estimated. The incident IBD in the high risk-window fulfilled both the primary and the study case definition, while thrombocytopenia and convulsion occurring in the high risk-window met only the primary case definition.

The incidence per 100,000 person years in the six months after vaccination with cTIV was 132.3 (95% CI 42.7, 410.3) for thrombocytopenia, 132.4 (42.7, 410.4) for convulsions and 44.1 (95% CI 6.2, 313.2) for incident IBD. In the sensitivity analysis using the stricter study case definition, the incidence per 100,000 person years in the six months post-vaccination with cTIV was 88.2 (95% CI 22.1, 352.7) for thrombocytopenia and 44.1 (95% CI 6.2, 313.2) for incident IBD. There were no outcomes of convulsions in the six-month period following cTIV that met the study case definition.

Since no studies of exacerbation of IBD or MS have been conducted using electronic primary health care data before, an algorithm was developed to identify such outcomes within THIN and validation with practice questionnaires was conducted. When the algorithm for the identification of IBD exacerbations was validated against exacerbations reported through the practice questionnaire the PPV was estimated at 0.10 (95% CI 0.01, 0.46). No PPV was estimated for MS because of low numbers of relapses. The Adjudication Committee concluded that the algorithm was not sufficiently accurate and reliable to identify such disease exacerbations and relapses within THIN and thus no analysis of IBD exacerbations and MS relapses was completed on the full THIN database. None of the IBD exacerbations or MS relapses identified on the questionnaire had a date of onset in the pre-defined high-risk windows following vaccination.

## 11.2 Limitations

A limitation of this analysis is that the study had a limited, and lower than planned, sample size, allowing exclusion of only a risk higher than originally planned. This is discussed in more detail in Section11.3.

The study uses an observational design. The major benefit of observational studies is that they reflect the routine clinical situation, taking into account the actual environment



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including patient profile, concomitant treatment, etc. One limitation of an observational database study is that the researcher can use only that information which has been collected for other purposes that may not be ideally suited to the testing of the study hypothesis. With regard to the exposure identification there may have been missed exposures because vaccination by employers or outside the primary care setting are not always captured by the primary care practice. However, population groups who are recommended to receive annual influenza vaccination are generally vaccinated by the general practitioner and as such this is not expected to affect generalizability to the routinely vaccinated population with influenza vaccines. While it may have reduced the numbers available for study it does not have implications for the analyses, as only exposed people were included.

For the outcomes of interest, the information available comprised that in the general practice record, including available correspondence from secondary care. The initial identification of the events was intentionally insensitive including unstructured text as well as coded entries to decrease the risk of false negatives. This allowed an Adjudication Committee to review each possible outcome against case definitions designed to be used with primary care records. As the Adjudication Committee was likely to be limited by information in the available records, some cases definitions required only the presence or absence of a diagnosis rather than to judge the accuracy of the diagnosis itself. The Adjudication Committee assigned a date of onset based on all available data in the medical records rather than the date of the first THIN entry. This should be a more accurate estimate of true onset as the initial symptoms could be taken into account. Additionally, the search for outcomes continued for 2 months after the end of follow-up (8 months search for 6 months post-exposure observation) to allow identification of those outcomes with a delayed diagnosis. However, for outcomes with longer lag times until clinical expression some misclassification may still be expected. If a delay in diagnosis extended beyond the eight months then this could result in a higher incidence of outcomes in the expected time but not the high risk-window, which is immediately post-exposure. The Adjudication Committee was blinded to date of exposure, so adjudication is expected to be non-differential.

The mean observation period was 272 days and thus reflected a reasonable complete follow-up after exposure across the cohort.

### 11.3 Interpretation

In the current study, the cohort consisted only of subjects exposed to cTIV seasonal influenza vaccination in a primary care setting. The majority of the study population was older than 60 and had chronic disease, as can be expected since seasonal influenza vaccination in the UK as provided in general practice is targeted at elderly above 65 years and specific groups who are at increased risk of complications of influenza disease.



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No episodes of first demyelinating events (including GBS), non-infectious encephalitis, or neuritis (optic and brachial) were identified in the observation period pre- or post-vaccination. With a sample size of 4578 it is possible to rule out a frequency for these outcomes of 1 in 1526 (an upper 95% confidence limit of 66 per 100,000) as per the rule of three described by Eypasch (Eypasch et al. 1995). For severe allergic reactions, Bell's palsy, paraesthesia and vasculitis, episodes were only observed in the expected time, but not in the high risk-window. Although the limitation of the small sample size remains, this observation further reduces the likelihood that any substantial risk exists for these outcomes following cTIV vaccination.

One event for each of the three following outcomes; thrombocytopenia, convulsions and incident IBD, occurred in the high risk-window when an event that was associated with cTIV would be expected to occur. The observed to expected ratio of 1.5 (95% CI 0.2, 14.9) for thrombocytopenia had a wide confidence interval which included one. The incidence of thrombocytopenia per 100,000 was 132.3 (95% CI 42.7, 410.3) in the six months after vaccination. An age standardized incidence rate of thrombocytopenia was estimated at 19.2 per 100,000 in the UK primary care population over 10 years (VAESCO 2011). Brighton case definitions appeared to be applied, but details of the methodology were limited and the results were noted to be preliminary. Another UK primary care database study, reported rates specifically for the sub-category of immune thrombocytopenia of 3.9 per 100,000 person-years (1990-2005) (Schoonen et al. 2009). The incidence rate varied by age and sex. In contrast, the current study included all thrombocytopenia identified by a wide range of codes as well as platelet values and text records. The one outcome of thrombocytopenia identified in the high risk-window did not match the stricter study case definition suggesting a degree of uncertainty around the diagnosis of this outcome. Therefore, on the basis of the observed versus expected analysis, it is considered that the data do not suggest any association for cTIV with thrombocytopenia.

One convulsion occurred in the high risk-window when a non-febrile convulsion with potential association with cTIV might be expected to occur. This outcome did not match the stricter study case definition. An observed to expected ratio of 3.3 (95% CI 0.3, 31.7) was found. Again the confidence interval was wide and overlapped one. The incidence rate for convulsions in six months after exposure was 132.4 (95% CI 42.7, 410.4) per 100,000 person years in our study. The age-adjusted incidence of all unprovoked seizures has been reported as 57 per 100,000 in the UK (MacDonald et al. 2000) but a binomial distribution has also been reported with rates in the elderly of 76 above 60 years of age and 147 per 100,000 above 70 years of age (Correll et al. 2014). Reported incidence rates of epilepsy in those over 65 years range between 70 and 240 per 100,000 person years (Correll et al. 2014). Two of four convulsions occurred in subjects with chronic disease. Additionally, some chronic diseases increase the risk of epilepsy (Rocca et al. 1987;



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Hauser et al. 1993). The incidence rate in the current study appears to be in line with the reported background incidence rate in the literature.

The third outcome with a date of onset within the high risk-window was an incident diagnosis of IBD. The event matched the study case definition, which required a secondary care diagnosis and 'evidence of capsule endoscopy or equivalent'. The IBD incidence of 44.1 per 100,000 in the six months after vaccination had a wide confidence interval (95% CI 6.2, 313.2). The incidence of IBD has been reported in the literature as 22 per 100,000 person years in the UK (Rubin et al. 2000) and, in the Netherlands, 46 per 100,000 in adults and 24 per 100,000 in the elderly (Jeuring et al. 2016). For IBD no observed versus expected ratio could be estimated in absence of episodes in the expected time. The single case of this rare outcome may have occurred by chance in the risk window. Comparison with background rates in the literature from similar settings and countries, does not indicate that the incidence of IBD observed during the post-vaccination period is higher than expected.

### 11.4 Generalizability

This observational study was based in primary care, the setting where most routine seasonal influenza vaccinations are given in the UK. The study included everyone who was exposed to cTIV provided they were permanently registered at a practice and were over 18 years of age in line with the licensed age indication. The results should be generalizable to UK adults who receive seasonal influenza vaccinations in this setting. The results may be generalizable on a wider geographic scale if that population vaccinated has a similar demographic and clinical profile, which is reasonably to be expected.

## 12. OTHER INFORMATION

The validation of the case identification for IBD exacerbations and MS relapses demonstrated the difficulties in the identification of periods of deterioration of these diseases using data sources such as the UK primary care databases.

First and second interim reports for this study have been submitted to PRAC on 22 April 2014 and 18 May 2015 respectively. The PRAC assessed both reports.

## 13. CONCLUSION

In conclusion, although the sample size was too small to rule out associations, the results from this general population study have not generated an hypothesis of an increased risk of the selected study outcomes after vaccination with cTIV.



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# APPENDICES

## Annex 1: List of stand-alone documents

None

## Annex 2: Analysis Plan Case Definitions and Risk Windows, Practice Questionnaires and Code Lists

### Table A 1: Case definitions for study outcomes

| Table A1 Case definitions for study outcomes |
|---|
| **Severe allergic reactions (Anaphylaxis, anaphylactoid reaction or angioedema)**<br><br>**Primary case definition:** Evidence of secondary care diagnosis, confirmation or treatment of an episode of anaphylaxis, anaphylactoid reaction, or severe angioedema (with respiratory/ airways involvement).<br><br>**Study case definition:**<br>***Anaphylaxis / anaphylactoid:***<br>•sudden onset AND rapid progression of signs and symptoms AND involving multiple (≥2) organ systems:<br>•≥1 major cardiovascular AND ≥1 major respiratory criterion<br>OR<br>≥1 major cardiovascular OR respiratory criterion AND<br>≥1 minor criterion involving ≥1 different system (other than cardiovascular or respiratory systems) OR<br>(≥1 major dermatologic) AND (≥1 minor cardiovascular AND/ OR minor respiratory criterion)<br>AND no alternative diagnosis for the event (Ruggeberg et al. 2007).<br>***Angioedema:*** an episode of severe angioedema (with respiratory / airways involvement) AND no alternative diagnosis for the event.<br><br>**Date of onset:** Date of 1st recorded symptom |
| **Bell's Palsy**<br><br>**Primary case definition**: An incident primary or secondary care diagnosis<br><br>**Study case definition:**<br>Has a sudden onset + shows initial rapid progression of symptoms and signs + shows resolution<br>AND<br>unexplained by review of clinical history and physical examination<br>AND<br>no alternative diagnosis for the event.<br><br>**Date of onset:** Date of diagnosis |



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**Table A1 Case definitions for study outcomes**

**Convulsions**

**Primary case definition**: An incident primary or secondary care diagnosis of seizure including those where there was no note of unconsciousness

**Study case definition:** An incident diagnosis of seizure, fit or convulsion whether or not this was febrile. Defined as history of unconsciousness AND other generalized motor manifestations with no alternative diagnosis for the event (Bonhoeffer et al. 2004).

Both case definitions classified an incident event as a 3 year seizure free period when off treatment.

**Exclusion**: for both primary and study definitions - events associated with an overdose of a drug known to cause seizure at high dose.

**Date of onset:** Date of 1st seizure.



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**Table A1 Case definitions for study outcomes Cont.**

**Demyelination including GBS and Fisher syndrome**

**Primary case definition**: An incident event with evidence that this was made or confirmed in secondary care.

**Study case definition:** An incident events: >2 attacks; clinical evidence of 1 lesion, with no alternative diagnosis for the event (Polman et al. 2011).
OR
fulfilling definition of ADEM, GBS or Fisher syndrome (see below).

**GBS:**
• Bilateral AND flaccid weakness of the limbs AND
• Decreased or absent deep tendon reflexes in weak limbs AND
• Monophasic illness pattern AND interval between onset and nadir of weakness between 12 hours and 28 days AND subsequent clinical plateau AND
• CSF total white cell count <50 cells/l (with or without CSF protein elevation above laboratory normal value) OR
• IF CSF not collected or results not available, electrophysiologic studies consistent with GBS AND
• Absence of identified alternative diagnosis for weakness (Sejvar et al. 2011).

**Fisher syndrome**
• Bilateral ophthalmoparesis AND bilateral reduced or absent tendon reflexes AND ataxia AND
• Absence of limb weakness AND
• Monophasic illness pattern AND interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau AND
• CSF with a total white cell count <50cells/ l]) (+ / - CSF protein elevation above laboratory normal value) OR
• Nerve conduction studies are normal, OR indicate involvement of sensory nerves only AND
• No alterations in consciousness or corticospinal tract signs AND
• Absence of identified alternative diagnosis (Sejvar et al. 2011).



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**Table A1 Case definitions for study outcomes Cont.**

**ADEM:** Level 1 of diagnostic certainty see (Sejvar et al. 2007):
(a) Demonstration of diffuse or multifocal areas of demyelination by histopathology.
OR
(b) Focal or multifocal findings referable to the central nervous system, including one or more of the following:
1. Encephalopathy
2. Focal cortical signs (including but not limited to: aphasia, alexia, agraphia, cortical blindness),
3. Cranial nerve abnormality/abnormalities, 4. Visual field defect/defects,
5. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex),
6. Motor weakness (either diffuse or focal; more often focal),
7. Sensory abnormalities (either positive or negative; sensory level),
8. Altered deep tendon reflexes (hypo- or hyperreflexia, asymmetry of reflexes), or
9. Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus,
AND
(c) Magnetic resonance imaging (MRI) findings displaying diffuse or multifocal white matter lesions on T2-weighted, diffusion-weighted (DWI), or fluid-attenuated inversion recovery (FLAIR) sequences (± gadolinium enhancement on T1 sequences),
AND
(d) Monophasic pattern to illness (i.e., absence of relapse within a minimum of 3 months of symptomatic nadir).
Exclusions for all encephalitis include another diagnosis for illness present or
Presence of a clear alternative acute infectious or other diagnosis for illness,
• Recurrence or relapse of illness at any point following a 3 month period of clinical improvement from symptomatic nadir, or
• If known, MRI findings or histopathologic data inconsistent with the diagnosis of ADEM.
For ADEM, recurrence or relapse of illness at any point following a 3 month period of clinical improvement from symptomatic nadir, or MRI findings or histopathologic data inconsistent with the diagnosis of ADEM.

**Date of onset:** date of 1st recorded symptom – for all demyelination

**Paraesthesia**

**Primary case definition**: An incident event with evidence that this was made or confirmed in secondary care.

**Study case definition:** A secondary care diagnosis of idiopathic paraesthesia with no later alternative reason for the paraesthesia; obvious exclusions are entrapment or obstruction such as carpel tunnel, or tingling due to herpes. Other exclusions are outcomes within other definitions: myelitis, ADEM, allergic reaction. Peripheral nerve neuropathy itself is not exclusion.

**Date of onset:** Date of 1st recorded symptom



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**Table A1 Case definitions for study outcomes Cont.**

**Non-infectious encephalitis**

**Primary case definition**: An incident event with evidence that this was made or confirmed in secondary care.

**Study case definition: see** (Sejvar et al. 2007)
**Encephalitis:**
Demonstration of acute inflammation of central nervous system parenchyma (± meninges) by histopathology, OR Encephalopathy (e.g. depressed or altered level of consciousness, lethargy, or personality change lasting >24 h),
AND ≥1 of the following:
1. Decreased or absent response to environment, as defined by response to loud noise or painful stimuli,
2. Decreased or absent eye contact,
3. Inconsistent or absent response to external stimuli,
4. Decreased arousability,
5. Seizure associated with loss of consciousness
OR
Focal or multifocal findings referable to the central nervous
system, including ≥1 of the following:
1. Focal cortical signs (including but not limited to: aphasia, alexia, agraphia, cortical blindness),
2. Cranial nerve abnormality/abnormalities,
3. Visual field defect/defect(s),
4. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex),
5. Motor weakness (either diffuse or focal; more often Focal)
6. Sensory abnormalities (either positive or negative; sensory level),
7. Altered deep tendon reflexes (hypo- or hyperreflexia, reflex asymmetry),
8. Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus.
AND
≥2 of the following indicators of inflammation of the CNS:
1. Fever (temperature ≥38 ◦ C),
2. CSF pleocytosis (>5WBC/mm3 in children >2 months of age; >15WBC/mm3 in children <2 months of age),
3. EEG findings consistent with encephalitis, or
4. Neuroimaging consistent with encephalitis.



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**Table A1 Case definitions for study outcomes Cont.**

**Non-infectious encephalitis cont.**

**Myelitis:** Level 1, or level 2 of diagnostic certainty with imaging as fever and CSF non-specific (e.g. abscess)
Demonstration of acute spinal cord inflammation (± meninges) by histopathology.
OR
(a) Myelopathy (development of sensory, motor, or autonomic
dysfunction attributable to the spinal cord, including upper- and/or lower-motor neuron weakness, sensory level, bowel and/or bladder dysfunction, erectile dysfunction).
AND
(b) ≤2 of the following indicators suggestive of spinal cord inflammation:
1. Fever (temperature ≥38 ◦C),
2. CSF pleocytosis (>5WBC/mm3 in children >2 months of age; >15WBC/mm3 in children <2 months of age),
3. Neuroimaging findings demonstrating acute inflammation (± meninges), or demyelination of the spinal cord.
Exclusions for all forms: An alternative diagnosis

**Date of onset:** Date of 1st recorded symptom for all non-infectious encephalitis

**Optic Neuritis**

**Primary case definition**: An incident event with evidence that this was made or confirmed in secondary care.

**Secondary case definition:** Incident event made or confirmed in secondary care when there is no alternative diagnosis for the event.

**Date of onset:** Date of diagnosis

**Brachial neuritis**

**Primary case definition**: An incident event with evidence that this was made or confirmed in secondary care.

**Study case definition:** Incident event made or confirmed in secondary care when there is no alternative diagnosis for the event.

**Date of onset:** Start of pain

**Vasculitis**

**Primary case definition**: An incident event AND evidence that this was made or confirmed in secondary care OR, for giant cell arteritis only, a primary care diagnosis, treated appropriately with subsequent resolution of symptoms.

**Study case definition:** Incident event diagnosed in secondary care
AND No alternative diagnosis for the event.

**Date of onset:** Date of 1st recorded symptom



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| **Table A1 Case definitions for study outcomes Cont.** |
|---|
| **Inflammatory bowel disease**<br>**Primary case definition**: Incident diagnosis with evidence that this was made or confirmed in secondary care.<br>**Study case definition:** Incident event and secondary care diagnosis and evidence of capsule endoscopy or equivalent.<br>Microscopic colitis is included in both definitions<br>**Date of onset:** Date of 1st recorded symptom |
| **Thrombocytopenia**<br>**Primary case definition**: Incident diagnosis of thrombocytopenia with evidence that this was made or confirmed in secondary care OR fulfilling the secondary case definition.<br>**Study case definition:** Platelet count $<150\times10^9$ L−1 AND confirmed by blood smear examination OR the presence of clinical signs and symptoms of spontaneous bleeding AND when the previous platelet count was $\geq150\times10^9$ L−1 (Wise et al. 2007). Events where the previous platelet count was <150×109 L−1 will be included if there is both a gap in time between measurements AND evidence that this is a new episode of thrombocytopenia.<br>Exclusion for both primary and study definitions – current chemotherapy or radiotherapy.<br>**Date of onset:** Earliest of 1st symptom or low platelet count |

## References to the Annex 2 Table A 1

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## Table A 2: Algorithm for identification of MS relapses and IBD exacerbations from THIN

**MS relapse**

A specific Read code for an MS relapse.
A Read code or text term for optic neuritis
A Read code for MS and, on the same day:

- a term for a relapse
- a code for a non-specific symptom
- recommended treatment

A text term for a non-specific symptom code and, on the same day a recommended treatment
A recommended treatment with no other indication in the electronic health record.

A recommended treatment was defined as either methylprednisolone or prednisolone orally daily dose ≥250mg, or oral dexamethasone daily dose ≥6mg.
A sensitivity analysis included methylprednisolone or dexamethasone regardless of dose.

**IBD exacerbation**

A specific Read code for an IBD exacerbation
A Read code for a specific GI symptom:

- rectal bleeding
- bloody diarrhoea
- mucus in faeces

A prescription of specific treatment for IBD (5-amonosalicylate after a 112 day gap or a glucocorticoid enema after a 30 day gap)
A record of IBD as a code or free text and one of the following on the same day:

- Code or free text for exacerbation (not specifically IBD exacerbation here)
- Code for a less specific GI symptom of an IBD exacerbation such as urgency, abdominal pain, diarrhoea
- Prescription for a new episode (after a 30 day gap) of a non-specific treatment
- Gastroenterology referral (a Read or NHS code).

A code for a non-specific GI symptom such as urgency or abdominal pain AND a prescription for a new episode of a non-specific treatment
A prescription for a new episode of treatment of a non-specific treatment but no other common indication

A non-specific treatment is defined as prednisolone or methylprednisolone orally daily dose ≥ 20 mg oral, or oral budesonide daily dose ≥9mg.
A sensitivity analysis included a prescription for a steroid treatment regardless of dose.



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**Table A 3**: **Post-exposure high (observed) and low risk-windows by outcome (days)**

| Outcome | High risk- window | Low risk-window |
|---|---|---|
| Severe allergic reactions | 0 – 1 | -14 – -1 |
| Bell's palsy | 1 – 90 | -60 – 0 |
| Convulsions (risk-window1) | 0 – 7 | -14 – -1 |
| Convulsions (risk-window 2) | 8 – 30‡ | -14 – -1 |
| First central nervous system demyelinating event* | 0 – 60 | -90 – -1 |
| GBS (risk-window 1) | 7 – 60‡ | -90 – 0 |
| GBS (risk-window 2) | 1 – 60 | -90 – 0 |
| Paraesthesia (risk-window 1) | 7 – 42‡ | -14 – 0 |
| Paraesthesia (risk-window 2) | 43 – 77‡ | -14 – 0 |
| Non-infectious encephalitis | 1 – 60 | -14 – 0 |
| Neuritis, (optic and brachial) | 1 – 42 | -30 – 0 |
| Vasculitis | 1 – 30 | -90 – 0 |
| IBD | 0 – 42 | -30 – -1 |
| Thrombocytopenia | 0 – 42 | -30 – -1 |
| IBD exacerbations | 1 – 42 | -30 – 0 |
| MS relapses | 1 – 60 | -90 - 0 |

GBS: Guillain-Barré syndrome ; IBD: inflammatory bowel disease ; MS : multiple sclerosis
*Includes GBS
‡Time between exposure (day 1 except for convulsions when day 2) and the start of high risk window is excluded.



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## Table A 4: Codes and text terms used in the identification of possible outcomes

| Read Code | Read Code Description | Text / therapy term |
|---|---|---|
| **A. Severe allergic reaction** | | |
| SN50.00 | Anaphylactic shock | anaphylact[b] |
| SN50000 | Anaphylactic shock due to adverse food reaction | angioedema[b] |
| SN50100 | Anaphy shock due/adv efect/correct drug or med proprly admin | angioneurotic oedema[c] |
| SN51.11 | Angioedema | anaphylax[b] |
| SN59300 | Anaphylactic shock due to bee sting | adrenaline[e] |
| SN59400 | Anaphylactic shock due to wasp sting | |
| SP0G.00 | Anaphylactoid reaction due to haemodialysis | |
| SP34.00 | Anaphylactic shock due to serum | |
| SN51.00 | Angioneurotic oedema | |
| SN50.11 | Anaphylaxis[f] | |
| **B. Allergy (included only if there was no code from list C on the same day)** | | |
| 2227.11 | O/E - allergic rash | allergic[a] |
| 66G4.00 | Allergy drug side effect | Not: allergic rhinitis, |
| 7Q08400 | Allergic emergency drugs Band 1 | allergic to egg, egg |
| H330.11 | Allergic asthma | allergy[c] |
| H33zz12 | Allergic asthma NEC | |
| H33zz13 | Allergic bronchitis NEC | |
| M280.00 | Allergic urticaria | |
| SN52.00 | Drug hypersensitivity NOS | |
| SN52.12 | Allergic drug reaction NOS | |
| SN52.12 | Allergic drug reaction NOS | |
| SN52.13 | Drug idiosyncrasy NOS | |
| SN53000 | Allergic reaction | |
| SN59.00 | Allergic reaction to venom | |
| SN59000 | Allergic reaction to bee sting | |
| SN59100 | Allergic reaction to insect bite | |
| SN59200 | Allergic reaction to wasp sting | |
| SN53200 | Allergic reaction to tattoo ink | |
| SN58B00 | Allergy to banana[f] | |
| 1Z4..00 | Allergic reaction to drug[h] | |
| 1Z4..11 | Drug allergy[h] | |
| **C. Allergy exclusions** | | |
| AB63300 | Allergic bronchopulmonary aspergillosis | |
| D403300 | Allergic eosinophilia | |
| F4C0611 | Acute allergic conjunctivitis | |
| F4C1400 | Other chronic allergic conjunctivitis | |
| F4C1411 | Allergic conjunctivitis | |
| F4D3100 | Contact or allergic eyelid dermatitis | |
| F4D3111 | Allergic dermatitis - eyelid | |
| H17..00 | Allergic rhinitis | |
| H17..12 | Allergic rhinosinusitis | |
| H170.00 | Allergic rhinitis due to pollens | |
| H171.00 | Allergic rhinitis due to other allergens | |
| H172.00 | Allergic rhinitis due to unspecified allergen | |

[a]A complete word. [b]Contains. [C]All words together (in any order). [d]All words in sequence. [e]As a prescription. [f]New Read code in study season 2. [g]Season 1 only. [h]New Read code in season 3.



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**Table A4 Codes and text terms used in the identification of possible outcomes cont.**

| Read Code | Read Code Description | Text / therapy term |
|---|---|---|
| **C. Allergy exclusions cont.** | | |
| H17z.00 | Allergic rhinitis NOS | |
| H35..00 | Extrinsic allergic alveolitis | |
| H35y.00 | Other allergic alveolitis | |
| H35yz00 | Other allergic alveolitis NOS | |
| H35z.00 | Allergic alveolitis and pneumonitis NOS | |
| H35z000 | Allergic extrinsic alveolitis NOS | |
| H35zz00 | Allergic alveolitis and pneumonitis NOS | |
| Hyu2000 | [X]Other seasonal allergic rhinitis | |
| Hyu2100 | [X]Other allergic rhinitis | |
| J072000 | Allergic parotitis | |
| J154000 | Allergic gastritis | |
| J432.00 | Allergic gastroenteritis and colitis | |
| J432.11 | Allergic diarrhoea | |
| J432000 | Allergic gastroenteritis | |
| J432100 | Allergic enteritis | |
| J432200 | Allergic enterocolitis | |
| J432300 | Allergic colitis | |
| J432z00 | Allergic gastroenteritis NOS | |
| M114.00 | Allergic (intrinsic) eczema | |
| M128.00 | Allergic contact dermatitis | |
| M128000 | Allergic contact dermatitis due to adhesives | |
| M128100 | Allergic contact dermatitis due to cosmetics | |
| M128200 | Allergic contact dermatitis due drugs in contact with skin | |
| M128300 | Allergic contact dermatitis due to dyes | |
| M128400 | Allergic contact dermatitis due to other chemical products | |
| M128500 | Allergic contact dermatitis due to food in contact with skin | |
| M128600 | Allergic contact dermatitis due to plants, except food | |
| M12A100 | Drug photoallergic response | |
| Myu2100 | [X]Allergic contact dermatitis due to oth chemical products | |
| Myu2300 | [X]Allergic contact dermatitis due to other agents | |
| N062.00 | Allergic arthritis | |
| N062000 | Allergic arthritis of unspecified site | |
| N062100 | Allergic arthritis of the shoulder region | |
| N062200 | Allergic arthritis of the upper arm | |
| N062300 | Allergic arthritis of the forearm | |
| N062400 | Allergic arthritis of the hand | |
| N062500 | Allergic arthritis of the pelvic region and thigh | |
| N062600 | Allergic arthritis of the lower leg | |
| N062700 | Allergic arthritis of the ankle and foot | |
| N062800 | Allergic arthritis of other specified site | |
| N062900 | Allergic arthritis of multiple sites | |
| N062z00 | Allergic arthritis NOS | |
| SN53300 | Atopy[f] | |
| 2126D00 | Cow's milk protein allergy symptoms resolved[f] | |
| 67I3000 | Education about weaning for cow's milk protein allergy[f] | |

[a]A complete word. [b]Contains. [c]All words together (in any order). [d]All words in sequence. [e]As a prescription. [f]New Read code in study season 2, [g]Season 1 only.



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**Table A4 Codes and text terms used in the identification of possible outcomes cont.**

| Read Code | Read Code Description | Text / therapy term |
|---|---|---|
| **D. Bell's palsy** | | |
| 1B32300 | Facial weakness | bells[a] |
| 2BR6.00 | O/E -cranial nerve 7-palsy-LMN | bell's[a] |
| 2BR7.00 | O/E -cranial 7 -paralysis -LMN | palsy[a] |
| 2BR9.00 | O/E - cranial 7 -paralysis-UMN | facial weakness[c] |
| F31..00 | Facial nerve disorders | cranial nerve[c] |
| F310.00 | Bell's (facial) palsy | cranial 7[c] |
| F31y.00 | Other facial nerve disorders | |
| F31yz00 | Other facial nerve disorder NOS | |
| F31z.00 | Facial nerve disorder NOS | |
| F32..00 | Other cranial nerve disorders | |
| F326.00 | Multiple cranial nerve palsies | |
| F326100 | Polyneuritis cranialis | |
| F326300 | Multiple cranial nerve palsies in sarcoidosis | |
| F326400 | Multiple cranial nerve palsies in neoplastic disease | |
| F326z00 | Multiple cranial nerve palsies NOS | |
| F32z.00 | Cranial nerve disorder NOS | |
| Fyu6400 | [X]Other cranial nerve disorders/other diseases CE | |
| SJ14.11 | Seventh cranial nerve injury | |
| **E. Convulsions** | | |
| 2822.00 | O/E - grand mal fit | convulsion[b] |
| 2823.00 | O/E - petit mal fit | seizure[b] |
| 2824.00 | O/E - focal (Jacksonian) fit | mal[g] |
| 2824.11 | O/E - Jacksonian fit | a fit[d] |
| 2824.12 | O/E - focal fit | epileptic fit[g] |
| 2825.00 | O/E - psychomotor fit | epileptic attack[g] |
| 2826.00 | O/E - salaam attack | epileptic[b] |
| 2827.00 | O/E - febrile convulsion | |
| 2828.00 | Absence seizure | |
| 1B26.00 | Trigger factor for seizure | |
| 1B27.00 | Seizures in response to acute event | |
| 1B63.00 | Had a fit | |
| 1B64.00 | Had a convulsion | |
| 1B64.11 | Convulsion - symptom | |
| 1B6B.00 | Febrile convulsion | |
| 282..00 | O/E - fit/convulsion | |
| 282..00 | O/E - fit/convulsion | |
| 282..11 | O/E - a convulsion | |
| 282..12 | O/E - a fit | |
| 282..13 | O/E - a seizure | |
| 282Z.00 | O/E - fit/convulsion NOS | |
| Eu10800 | [X]Alcohol withdrawal-induced seizure | |
| Eu44500 | [X]Dissociative convulsions | |
| F251200 | Epileptic seizures - clonic | |

[a]A complete word. [b]Contains. [c]All words together (in any order). [d]All words in sequence. [e]As a prescription. [f]New Read code in study season 2. [g]Season 1 only.



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**Table A4 Codes and text terms used in the identification of possible outcomes cont.**

| Read Code | Read Code Description | Text / therapy term |
|---|---|---|
| **E. Convulsions cont.** | | |
| F132z12 | Myoclonic seizure | |
| F250200 | Epileptic seizures - atonic | |
| F250300 | Epileptic seizures - akinetic | |
| F251300 | Epileptic seizures - myoclonic | |
| F251400 | Epileptic seizures - tonic | |
| F251600 | Grand mal seizure | |
| F254500 | Complex partial epileptic seizure | |
| F255600 | Simple partial epileptic seizure | |
| R003.00 | [D]Convulsions | |
| R003000 | [D]Convulsions, febrile | |
| R003011 | [D]Pyrexial convulsion | |
| R003300 | [D]Reflex anoxic seizure | |
| R003400 | [D]Nocturnal seizure | |
| R003y00 | [D]Other specified convulsion | |
| R003z00 | [D]Convulsion NOS | |
| R003z11 | [D]Seizure NOS | |
| Ryu7100 | [X]Other and unspecified convulsions | |
| 1JA0.00 | Suspected epilepsy | |
| 1O30.00 | Epilepsy confirmed | |
| 6671.00 | Initial epilepsy assessment | |
| 667B.00 | Nocturnal epilepsy | |
| 8Hlp.00 | Referral to epilepsy clinic | |
| F250.00 | Generalised nonconvulsive epilepsy | |
| F250000 | Petit mal (minor) epilepsy | |
| F250y00 | Other specified generalised nonconvulsive epilepsy | |
| F250z00 | Generalised nonconvulsive epilepsy NOS | |
| F251.00 | Generalised convulsive epilepsy | |
| F251000 | Grand mal (major) epilepsy | |
| F251011 | Tonic-clonic epilepsy | |
| F251500 | Tonic-clonic epilepsy | |
| F251y00 | Other specified generalised convulsive epilepsy | |
| F251z00 | Generalised convulsive epilepsy NOS | |
| F254.00 | Partial epilepsy with impairment of consciousness | |
| F254000 | Temporal lobe epilepsy | |
| F254100 | Psychomotor epilepsy | |
| F254200 | Psychosensory epilepsy | |
| F254300 | Limbic system epilepsy | |
| F254z00 | Partial epilepsy with impairment of consciousness NOS | |
| F255.00 | Partial epilepsy without impairment of consciousness | |
| F255000 | Jacksonian, focal or motor epilepsy | |
| F255011 | Focal epilepsy | |
| F255012 | Motor epilepsy | |

[a]A complete word. [b]Contains. [c]All words together (in any order). [d]All words in sequence. [e]As a prescription. [f]New Read code in study season 2. [g]Season 1 only.



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**Table A4 Codes and text terms used in the identification of possible outcomes cont.**

| Read Code | Read Code Description | Text / therapy term |
|---|---|---|
| **E. Convulsions cont.** | | |
| F255100 | Sensory induced epilepsy | |
| F255200 | Somatosensory epilepsy | |
| F255300 | Visceral reflex epilepsy | |
| F255311 | Partial epilepsy with autonomic symptoms | |
| F255400 | Visual reflex epilepsy | |
| F255500 | Unilateral epilepsy | |
| F255y00 | Partial epilepsy without impairment of consciousness OS | |
| F255z00 | Partial epilepsy without impairment of consciousness NOS | |
| F257.00 | Kojevnikov's epilepsy | |
| F25A.00 | Juvenile myoclonic epilepsy | |
| F25B.00 | Alcohol-induced epilepsy | |
| F25C.00 | Drug-induced epilepsy | |
| F25D.00 | Menstrual epilepsy | |
| F25E.00 | Stress-induced epilepsy | |
| F25F.00 | Photosensitive epilepsy | |
| F25y.00 | Other forms of epilepsy | |
| F25y000 | Cursive (running) epilepsy | |
| F25y100 | Gelastic epilepsy | |
| F25y400 | Benign Rolandic epilepsy | |
| F25yz00 | Other forms of epilepsy NOS | |
| F25z.00 | Epilepsy NOS | |
| Fyu5000 | [X]Other generalized epilepsy and epileptic syndromes | |
| Fyu5100 | [X]Other epilepsy | |
| SC20000 | Traumatic epilepsy | |
| F250.00 | Generalised nonconvulsive epilepsy | |
| F254300 | Limbic system epilepsy | |
| **F. Demyelination** | | |
| F20..00 | Multiple sclerosis | demyelin[b] |
| F20..11 | Disseminated sclerosis | multiple sclerosis[d] |
| F200.00 | Multiple sclerosis of the brain stem | guillain[a] |
| F201.00 | Multiple sclerosis of the spinal cord | schilder[a] |
| F202.00 | Generalised multiple sclerosis | schilders[a] |
| F204.00 | Benign multiple sclerosis | schilder's[a] |
| F205.00 | Malignant multiple sclerosis | balos[a] |
| F206.00 | Primary progressive multiple sclerosis | balo's[a] |
| F20z.00 | Multiple sclerosis NOS | marchiafava[a] |
| F21..00, | Other central nervous system demyelinating diseases | fisher[a] |
| F211.00 | Schilder's disease | bignami[a] |
| F211.11 | Balo's concentric sclerosis | barre[a] |
| F213.00 | Clinically isolated syndrome | myelitis[g] |
| F21X.00 | Acute disseminated demyelination, unspecified | polyneuritis[a] |

[a]A complete word. [b]Contains. [C]All words together (in any order). [d]All words in sequence. [e]As a prescription. [f]New Read code in study season 2. [g]Season 1 only.



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**Table A4 Codes and text terms used in the identification of possible outcomes cont.**

| Read Code | Read Code Description | Text / therapy term |
|---|---|---|
| **F. Demyelination cont.** | | |
| F21y.00 | Other specified central nervous system demyelinating disease | |
| F21y000 | Marchiafava-Bignami disease | |
| F21y100 | Central pontine myelinosis | |
| F21y300 | Central demyelination of corpus callosum | |
| F21y400 | Subacute necrotizing myelitis | |
| F21y500 | Concentric sclerosis | |
| F21y600 | Vanishing white matter disease | |
| F21yz00 | Other specified central nervous system demyelination NOS | |
| F21z.00 | Central nervous system demyelination NOS | |
| F370.00 | Acute infective polyneuritis | |
| F370000 | Guillain-Barre syndrome | |
| F370100 | Postinfectious polyneuritis | |
| F370200 | Miller-Fisher syndrome | |
| F370z00 | Acute infective polyneuritis NOS | |
| Fyu4.00 | [X]Demyelinating diseases of the central nervous system | |
| Fyu4000 | [X]Other specified acute disseminated demyelination | |
| Fyu4100 | [X]Other specified demyelinating diseases/the CNS | |
| Fyu4200 | [X]Acute disseminated demyelination, unspecified | |
| 1JA3.00 | Suspected multiple sclerosis | |
| **G. Paraesthesia** | | |
| 1B41.00 | Has pins and needles | pins, needles[b] |
| 1B42.00 | Has prickling sensation | prickling[a] |
| 1B43.00 | Has tingling sensation | tingling[a] |
| 1B46.00 | C/O paraesthesia | paraesthesia[b] |
| 1B47.00 | Transient paraesthesia | formication[a] |
| 29B5.00 | O/E - paraesthesia present | |
| 29B5000 | O/E - paraesthesia in hands | |
| G73y400 | Acroparaesthesia - Schultze's type | |
| G73y411 | Schultze's simple acroparaesthesia | |
| G73y500 | Acroparaesthesia - Nothnagel's type | |
| G73y511 | Nothnagel's vasomotor acroparaesthesia | |
| G73y600 | Acroparaesthesia - unspecified | |
| R020100 | [D]Burning of skin | |
| R020200 | [D]Pricking of skin | |
| R020300 | [D]Tingling of skin | |
| R020700 | [D]Paraesthesia | |
| R020800 | [D]Formication | |
| R020z00 | [D]Skin sensation disturbance NOS | |
| Ryu2000 | [X]Other and unspecified disturbances of skin sensation | |
| Ryu5400 | [X]Oth & unspec sympt/sign involv gen sensations/perceptns | |

[a]A complete word. [b]Contains. [C]All words together (in any order). [d]All words in sequence. [e]As a prescription. [f]New Read code in study season 2. [g]Season 1 only.



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**Table A4 Codes and text terms used in the identification of possible outcomes cont.**

| Read Code | Read Code Description | Text / therapy term |
|---|---|---|
| **H. Encephalitis** | | |
| A136z00 | Tuberculous encephalitis or myelitis NOS | rasmussen[a] |
| A413.00 | Progressive multifocal leucoencephalopathy | encephalitis[b] |
| A413.11 | Progressive multifocal leukoencephalopathy | encephalopathy[b] |
| A4zy100 | Acute necrotising encephalitis | |
| A4zy200 | Epidemic encephalitis | |
| A4zy300 | Encephalitis lethargica | |
| A4zy400 | Von Economo's encephalitis | |
| A520.00 | Postvaricella encephalitis | |
| C253.00 | Wernicke's encephalopathy | |
| F03..00 | Encephalitis, myelitis and encephalomyelitis | |
| F03..11 | Encephalomyelitis | |
| F03..12 | Myelitis | |
| F03..13 | Transverse myelitis | |
| F034.00 | Postimmunisation encephalitis | |
| F034000 | Post BCG vaccination encephalitis | |
| F034100 | Post typhoid vaccination encephalitis | |
| F034200 | Post paratyphoid vaccination encephalitis | |
| F034300 | Post cholera vaccination encephalitis | |
| F034400 | Post plague vaccination encephalitis | |
| F034500 | Post tetanus vaccination encephalitis | |
| F034600 | Post diphtheria vaccination encephalitis | |
| F034700 | Post pertussis vaccination encephalitis | |
| F034800 | Post smallpox vaccination encephalitis | |
| F034900 | Post rabies vaccination encephalitis | |
| F034A00 | Post typhus vaccination encephalitis | |
| F034B00 | Post yellow fever vaccination encephalitis | |
| F034C00 | Post measles vaccination encephalitis | |
| F034D00 | Post polio vaccination encephalitis | |
| F034E00 | Post mumps vaccination encephalitis | |
| F034F00 | Post rubella vaccination encephalitis | |
| F034G00 | Post influenza vaccination encephalitis | |
| F034H00 | Post hepatitis A vaccination encephalitis | |
| F034J00 | Post hepatitis B vaccination encephalitis | |
| F034x00 | Post mixed vaccination encephalitis | |
| F034y00 | Post other specified vaccination encephalitis | |
| F034z00 | Postimmunisation encephalitis NOS | |
| F035.00 | Postinfectious encephalitis | |
| F035200 | Rasmussen syndrome | |
| F036.00 | Toxic encephalitis | |
| F036000 | Toxic encephalitis due to lead | |
| F036100 | Toxic encephalitis due to mercury | |
| F03y.00 | Other causes of encephalitis | |

[a]A complete word. [b]Contains. [c]All words together (in any order). [d]All words in sequence. [e]As a prescription. [f]New Read code in study season 2. [g]Season 1 only.



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**Table A4 Codes and text terms used in the identification of possible outcomes cont.**

| Read Code | Read Code Description | Text / therapy term |
|---|---|---|
| **H. Encephalitis cont.** | | |
| F036200 | Toxic encephalitis due to thallium | |
| F036z00 | Toxic encephalitis NOS | |
| F037.00 | Transverse myelitis | |
| F037000 | Varicella transverse myelitis | |
| F03X.00 | Bacterial meningoencephalitis+meningomyelitis,NEC | |
| F03y.11 | Encephalomyelitis NOS | |
| F03y.11 | Encephalomyelitis NOS | |
| F03z.00 | Encephalitis NOS | |
| F03z.11 | Encephalomyelitis NOS | |
| F11x011 | Alcoholic encephalopathy | |
| F11x800 | Cerebral degeneration due to multifocal leucoencephalopathy | |
| F132200 | Myoclonic encephalopathy | |
| F283.00 | Unspecified encephalopathy | |
| Fyu0600 | [X]Other encephalitis, myelitis and encephalomyelitis | |
| Fyu0700 | [X]Encephalitis,myelitis+encephalomyelitis/bactrl disease CE | |
| Fyu0800 | [X]Encephalitis,myelitis+encephalomyelitis/viral disease CE | |
| Fyu0900 | [X]Encephl,myelitis+encphmylitis/oth infct+parasit diseas CE | |
| Fyu0A00 | [X]Encephalitis,myelitis+encephalomyelitis/other diseases CE | |
| H27y000 | Influenza with encephalopathy | |
| Q437000 | Bilirubin encephalopathy | |
| F212.00 | Acute and subacute haemorrhagic leukoencephalitis [Hurst] | |
| **I. Optic and brachial neuritis** | | |
| A36y000 | Meningococcal optic neuritis | retrobulbar neuritis[b] |
| A94y400 | Syphilitic retrobulbar neuritis | optic neuritis[b] |
| F4H3.00 | Optic neuritis | optic papillitis[b] |
| F4H3000 | Unspecified optic neuritis | neuromyelitis optica[b] |
| F4H3100 | Optic papillitis | devic's[b] |
| F4H3200 | Acute retrobulbar neuritis | devic[a] |
| F4H3z00 | Optic neuritis NOS | devics[a] |
| FyuJ100 | [X]Retrobulbar neuritis in diseases classified elsewhere | brachial neuritis[c] |
| F210.00 | Neuromyelitis optica | neuralgic amyotrophy[c] |
| F210.11 | Devic's disease | parsonage syndrome[b] |
| N134.00 | Brachial (cervical) neuritis | cervical neuritis[c] |
| F335.00 | Neuralgic amyotrophy | |
| F335.11 | Parsonage - Aldren - Turner syndrome | |

[a]A complete word. [b]Contains. [c]All words together (in any order). [d]All words in sequence. [e]As a prescription. [f]New Read code in study season 2. [g]Season 1 only.



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**Table A4 Codes and text terms used in the identification of possible outcomes cont.**

| Read Code | Read Code Description | Text / therapy term |
|---|---|---|
| **J. Vasculitis** | | |
| AD61.00 | Behcet's syndrome | arteritis[b] |
| C332000 | Cryoglobulinaemic purpura | vasculit[b] |
| C332100 | Cryoglobulinaemic vasculitis | kawasaki[b] |
| D310.00 | Allergic purpura | behcet[b] |
| D310000 | Henoch-Schonlein purpura | angiitis[b] |
| D310011 | Anaphylactoid purpura | wegener[b] |
| D310012 | Acute vascular purpura | cryoglobulinaemi[b] |
| D310100 | Henoch-Schonlein nephritis | takayasu[b] |
| D310z00 | Allergic purpura NOS | pulseless[a] |
| F371100 | Polyneuropathy in polyarteritis nodosa | strauss[b] |
| F396300 | Myopathy due to polyarteritis nodosa | arteritis[b] |
| F421D00 | Eales' disease | henoch[b] |
| F421E00 | Retinal vasculitis NOS | aortitis[a] |
| G42y000 | Pulmonary arteritis | vasculopathy[a] |
| G674.00 | Cerebral arteritis | horton[b] |
| G75..00 | Polyarteritis nodosa and allied conditions | lethal midline granuloma[b] |
| G750.00 | Polyarteritis nodosa | antiglomerular basement membrane[c] |
| G750.11 | Necrotising angiitis | goodpasture[b] |
| G751.00 | Acute febrile mucocutaneous lymph node syndrome | mucocutaneous lymph node[b] |
| G751000 | Kawasaki disease | eales[a] |
| G751z00 | Acute febrile mucocutaneous lymph node syndrome NOS | eales'[a] |
| G752.00 | Hypersensitivity angiitis | eale's[a] |
| G752.11 | Hypersensitivity arteritis | purpura[a] |
| G752000 | Goodpasture's syndrome | granulomatosis[a] |
| G752100 | Goodpasture's disease | eosinophili[b] |
| K01x300 | Nephrotic syndrome in polyarteritis nodosa | |
| K425200 | Ulceration of vulva in Behcet's disease | |
| M152.11 | Nodular vasculitis | |
| M2y0200 | Livedoid vasculitis | |
| M2y0X00 | Vasculitis limited to skin, unspecified | |
| Myu7A00 | [X]Other vasculitis limited to the skin | |
| Myu7G00 | [X]Vasculitis limited to skin, unspecified | |
| N012.00 | Arthropathy in Behcet's syndrome | |
| N012000 | Arthropathy in Behcet's syndrome of unspecified site | |
| N012011 | Behcet's syndrome arthropathy | |
| N012100 | Arthropathy in Behcet's syndrome of the shoulder region | |
| N012200 | Arthropathy in Behcet's syndrome of the upper arm | |
| N012300 | Arthropathy in Behcet's syndrome of the forearm | |

[a]A complete word. [b]Contains. [c]All words together (in any order). [d]All words in sequence. [e]As a prescription. [f]New Read code in study season 2. [g]Season 1 only.



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**Table A4 Codes and text terms used in the identification of possible outcomes cont.**

| Read Code | Read Code Description | Text / therapy term |
|---|---|---|
| **J. Vasculitis cont.** | | |
| N012400 | Arthropathy in Behcet's syndrome of the hand | |
| N012500 | Arthropathy in Behcet's syndrome of the pelvis/thigh | |
| N012600 | Arthropathy in Behcet's syndrome of the lower leg | |
| N012700 | Arthropathy in Behcet's syndrome of the ankle and foot | |
| N012x00 | Arthropathy in Behcet's syndrome of multiple sites | |
| N012y00 | Arthropathy in Behcet's syndrome of other specified sites | |
| N012z00 | Arthropathy in Behcet's syndrome NOS | |
| N040N00 | Rheumatoid vasculitis | |
| N200.00 | Giant cell arteritis with polymyalgia rheumatica | |
| Nyu4000 | [X]Other conditions related to polyarteritis nodosa | |
| Nyu4100 | [X]Other giant cell arteritis | |
| C330100 | Benign primary hypergammaglobulinaemic purpura | |
| C37y100 | Eosinophilic granuloma | |
| A931.00 | Syphilitic aortitis | |
| G767.00 | Aortitis - syphilitic | |
| G754.11 | Granulomatosis with polyangiitis[f] | |
| K036.00 | Cryoglobulinaemic glomerulonephritis[f] | |
| M2y2600 | Dystrophic calcification of skin[f] | |
| M2y9100 | Cutaneous amyloidosis[f] | |
| **K. Inflammatory bowel disease** | | |
| J4...00 | Noninfective enteritis and colitis | colitis[b] |
| J4...11 | Colitis - noninfective | ibd[b] |
| J4...12 | Inflammatory bowel disease | inflammatory bowel[c] |
| J40..00 | Regional enteritis - Crohn's disease | regional enteritis[c] |
| J40..11 | Crohn's disease | crohn's |
| J40..12 | Granulomatous enteritis | crohns |
| J400.00 | Regional enteritis of the small bowel | crohn |
| J400000 | Regional enteritis of the duodenum | enteritis |
| J400100 | Regional enteritis of the jejunum | proctitis |
| J400200 | Crohn's disease of the terminal ileum | toxic megacolon[c] |
| J400300 | Crohn's disease of the ileum unspecified | ileitis |
| J400400 | Crohn's disease of the ileum NOS | sigmoiditis |
| J400z00 | Crohn's disease of the small bowel NOS | ulcerative |
| J401.00 | Regional enteritis of the large bowel | aminosalicylate[e] |
| J401000 | Regional enteritis of the colon | |
| J401100 | Regional enteritis of the rectum | |
| J401z00 | Crohn's disease of the large bowel NOS | |
| J401z11 | Crohn's colitis | |
| J402.00 | Regional ileocolitis | |
| J40z.00 | Regional enteritis NOS | |

[a]A complete word. [b]Contains. [c]All words together (in any order). [d]All words in sequence. [e]As a prescription. [f]New Read code in study season 2. [g]Season 1 only.



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**Table A4 Codes and text terms used in the identification of possible outcomes cont.**

| Read Code | Read Code Description | Text / therapy term |
|---|---|---|
| **K. Inflammatory bowel disease cont.** | | |
| J40z.11 | Crohn's disease NOS | |
| J41..00 | Idiopathic proctocolitis | |
| J41..11 | Mucous colitis and/or proctitis | |
| J41..12 | Ulcerative colitis and/or proctitis | |
| J410.00 | Ulcerative proctocolitis | |
| J410000 | Ulcerative ileocolitis | |
| J410100 | Ulcerative colitis | |
| J410200 | Ulcerative rectosigmoiditis | |
| J410300 | Ulcerative proctitis | |
| J410400 | Exacerbation of ulcerative colitis | |
| J411.00 | Ulcerative (chronic) enterocolitis | |
| J412.00 | Ulcerative (chronic) ileocolitis | |
| J413.00 | Ulcerative pancolitis | |
| J41y.00 | Other idiopathic proctocolitis | |
| J08z900 | Orofacial Crohn's disease | |
| J41y011 | Inflammatory polyps of colon | |
| J41y100 | Toxic megacolon | |
| J41yz00 | Other idiopathic proctocolitis NOS | |
| J41z.00 | Idiopathic proctocolitis NOS | |
| J43..00 | Other non-infective inflammatory gastroenteritis and colitis | |
| J43..12 | Enterocolitis | |
| J6A..00 | Gastroenteritis and colitis of unknown origin | |
| J410z00 | Ulcerative proctocolitis NOS | |
| J431200 | Toxic enterocolitis | |
| J431300 | Toxic colitis | |
| J432.00 | Allergic gastroenteritis and colitis | |
| J432200 | Allergic enterocolitis | |
| J432300 | Allergic colitis | |
| J433200 | Dietetic enterocolitis | |
| J433300 | Dietetic colitis | |
| J434.00 | Pseudomembranous colitis | |
| J436.00 | Microscopic colitis | |
| J436000 | Collagenous colitis | |
| J436100 | Lymphocytic colitis | |
| J437.00 | Colitis | |
| J438.00 | Left sided colitis | |
| J43z.00 | Other non-infective gastroenteritis and colitis NOS | |
| J4z3.00 | Non-infective colitis NOS | |
| J4z6.00 | Indeterminate colitis | |
| Jyu4.00 | [X]Noninfective enteritis and colitis | |
| 8Cc5.00 | Management of inflammatory bowel disease | |
| 8Cc5.11 | Management of ibd (inflammatory bowel disease) | |

[a]A complete word. [b]Contains. [C]All words together (in any order). [d]All words in sequence. [e]As a prescription. [f]New Read code in study season 2. [g]Season 1 only.



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**Table A4 Codes and text terms used in the identification of possible outcomes cont.**

| Read Code | Read Code Description | Text / therapy term |
|---|---|---|
| **K. Inflammatory bowel disease cont.** | | |
| Jyu4000 | [X]Other Crohn's disease | |
| Jyu4100 | [X]Other ulcerative colitis | |
| Jyu4200 | [X]Other specified noninfective gastroenteritis+colitis | |
| J4z2.00 | Non-infective ileitis NOS | |
| J4z4.00 | Non-infective sigmoiditis NOS | |
| **L. Thrombocytopenia** | | |
| 42P2.00 | Thrombocytopenia | thrombocytopeni[b] |
| 42P2.11 | Auto-immune thrombocytopenia | hellp |
| 42P4.00 | Platelet count abnormal | |
| C391211, | Thrombocytopenic eczema with immunodeficiency | |
| D313.00 | Primary thrombocytopenia | |
| D313.11 | Evan's syndrome | |
| D313.12 | Idiopathic thrombocytopenic purpura | |
| L12A.00 | HELLP - Syndrome haemolysis, elev liver enzyme low platelets | |
| D313.15 | Thrombocytopenic purpura | |
| D313000 | Idiopathic thrombocytopenic purpura | |
| D313012 | ITP - idiopathic thrombocytopenic purpura | |
| D313111 | Hereditary thrombocytopenia NEC | |
| D313300 | [X]Essential thrombocytopenia NOS | |
| D313y00 | Other specified primary thrombocytopenia | |
| D313z00 | Primary thrombocytopenia NOS | |
| D313z11 | Essential thrombocytopenia NOS | |
| D314.00 | Secondary thrombocytopenia | |
| D314100 | Thrombocytopenia due to drugs | |
| D314y00 | Other specified secondary thrombocytopenia | |
| D314z00 | Secondary thrombocytopenia NOS | |
| D314z11 | Dilutional thrombocytopenia | |
| D315.00 | Thrombocytopenia NOS | |
| Dyu3200 | [X]Other primary thrombocytopenia | |
| G756100, | Thrombotic thrombocytopenic purpura | |
| D314011 | Thrombocytopenia due to massive blood transfusion | |
| D314300 | Heparin-induced thrombocytopenia | |
| D314200 | Thrombocytopenia due to extracorporeal circulation of blood | |
| D314000 | Post-transfusion purpura | |
| D314300 | Heparin-induced thrombocytopenia | |
| 42P..00 | Platelet count | + result was $<15010^9$/L |

[a]A complete word. [b]Contains. [c]All words together (in any order). [d]All words in sequence. [e]As a prescription. [f]New Read code in study season 2. [g]Season 1 only.



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**Figure A 1: Practice questionnaires for the validation of MS relapses and IBD exacerbations**

Multiple Sclerosis relapses

| Practice ID | Patient ID | | Sex | Year of birth | Start Date | End date |
|---|---|---|---|---|---|---|
| | | | | | | |

*This patient has an electronic record of a diagnosis of multiple sclerosis (MS). We would like to know if they had any relapses of their MS on or between the start and end dates listed above.*

**We are interested in information in the free text and correspondence (electronic, scanned or paper) as well that on the main patient record. We may not have access to this information. If the patient has left the practice please send any information that you still have access to.**

1. Did the patient consult with an episode of MS relapse which began on or between the start and end date given above? Relapses mostly occur in relapsing /remitting MS but may be seen in MS that is categorised as progressive (either primary or secondary). A **relapse** is defined as:

   The occurrence, recurrence or worsening of symptoms of neurological dysfunction:

   - of greater than 24 hours duration,
   - started at least 30 days after the previous relapse,
   - ended (or is expected to end) with a remission which is partial or complete,
   - **NOT** including fatigue alone or transient fever-related worsening of symptoms.

   Symptoms of an exacerbation might include, but are not limited to, focal limb weakness or clumsiness; bladder, bowel, swallowing or speech problems; eye pain and vision problems; cranial nerve events, numbness or deafness. Please include any relevant contact with the practice or with secondary care.

   ☐ No, the patient did not consult for an MS relapse starting on or between the dates given above. (Please return the questionnaire to the address below)

   ☐ Yes, the patient consulted for an MS relapse – please complete the details below for each episode of relapse.

| Date of the initial symptom of relapse | Presenting clinical symptom | Initial prescription treatment, if any. Please state if none prescribed |
|---|---|---|
| | | |
| | | |
| | | |
| | | |

Additional space overleaf

Many thanks for your time in completing this questionnaire.

Please return using the enclosed label

**Researcher's Ref:**

Cegedim Strategic Data (THIN)
Additional Information Services from THIN, 1 Canal Side Studios, 8-14 St Pancras Way, London NW1 0QG
Registered Number 04396589 **Telephone**: +44 (0)20 7388 8215 **Facsimile**: +44 (0)20 7388 8492



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## Figure A1 Validation questionnaires cont.

**IBD Exacerbations**

| Practice ID | Patient ID | Sex | Year of Birth | Start Date | End date |
|---|---|---|---|---|---|
| | | | | | |

This patient has an electronic record of inflammatory bowel disease (IBD). We would like to know if they had any exacerbations of their IBD on or between the start and end dates listed above.

**We are interested in information in the free text and correspondence (electronic, scanned or paper) as well that on the main patient record. We may not have access to this information. If the patient has left the practice please send any information that you still have.**

1. Did the patient consult with an episode of IBD exacerbation which began on or between the start and end date given above? An exacerbation is defined as:

   The occurrence, recurrence or worsening of symptoms of IBD which lasted for longer than 24 hours AND began at least 30 days after the last exacerbation. Symptoms of an exacerbation might include, but are not limited to; abdominal cramps/pain, diarrhoea, blood in stools, urgency to have bowel movements. Please include any contact with the practice or with secondary care.

   ☐ No, the patient did not consult for an IBD exacerbation starting on or between the dates given above.

   ☐ Yes, the patient consulted for an IBD exacerbation – please complete the details below for each episode of an exacerbation.

| Date of the initial symptom of exacerbation | Presenting clinical symptom | Initial prescription treatment, if any. Please state if none prescribed |
|---|---|---|
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

Additional space overleaf

Many thanks for your time in completing this questionnaire.

Please return using the enclosed label

**Researcher's Ref:**

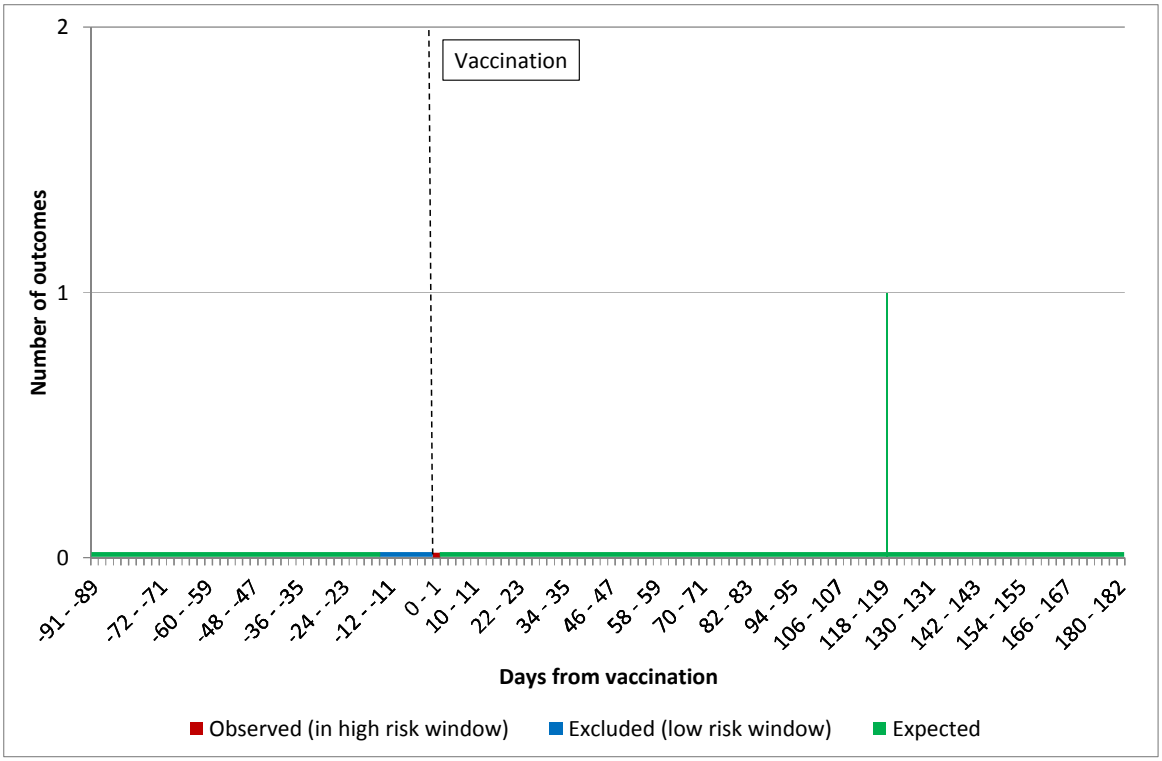
Cegedim Strategic Data (THIN)
Additional Information Services from THIN, 1 Canal Side Studios, 8-14 St Pancras Way, London NW1 0QG
Registered Number 04396589 **Telephone:** +44 (0)20 7388 8215 **Facsimile:** +44 (0)20 7388 8492



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## Annex 3: Plots of Time From cTIV Exposure To Onset Of Outcome

**Figure B 1**: **Distribution of severe allergic reactions by time from cTIV exposure**

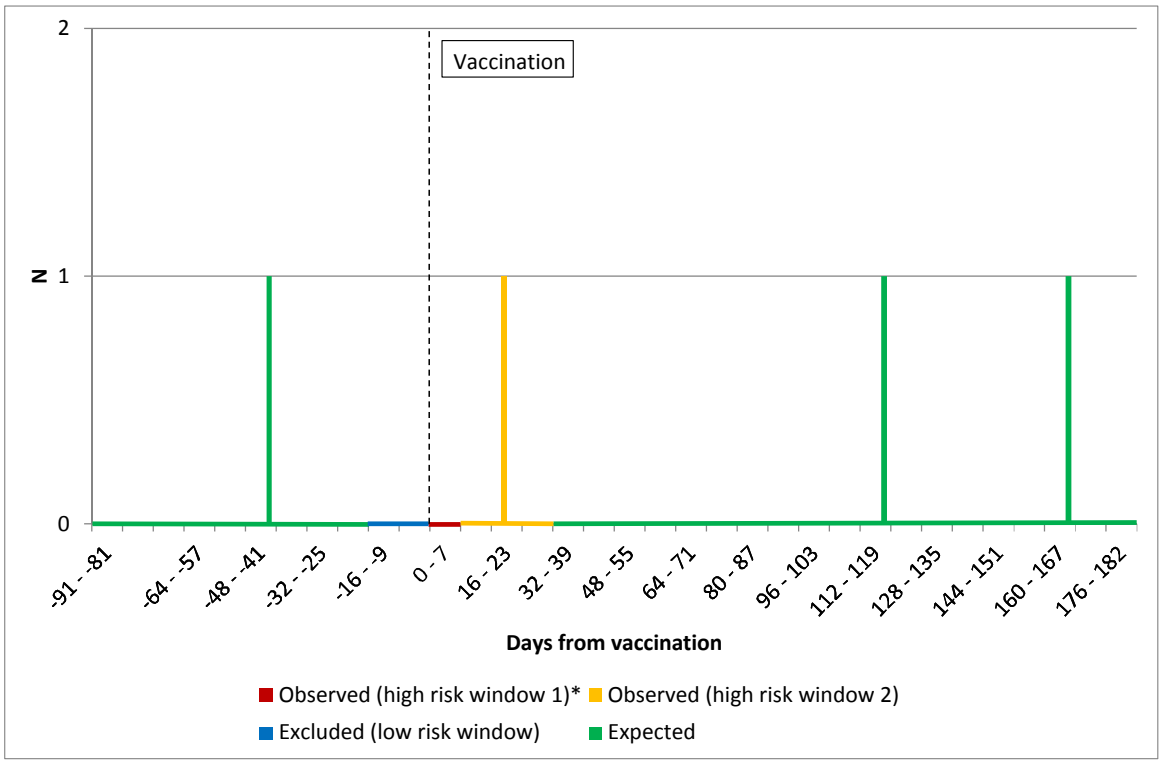



Uses the primary case definition. For explanation of the observed, excluded and expected time periods see Section 9.8.3 including Figure 2. Outcomes within each period are denoted by colour (see legend): the high risk window = days 0 – 1, and the excluded low risk window = days -14 to -1, where day 0 is the date of cTIV exposure (vaccination). The study period is spilt into 2 day periods except for the first window (-91 to -89 days) and the last window (180 to 182 days).



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**Figure B 2**: **Distribution of convulsions by time from cTIV exposure**

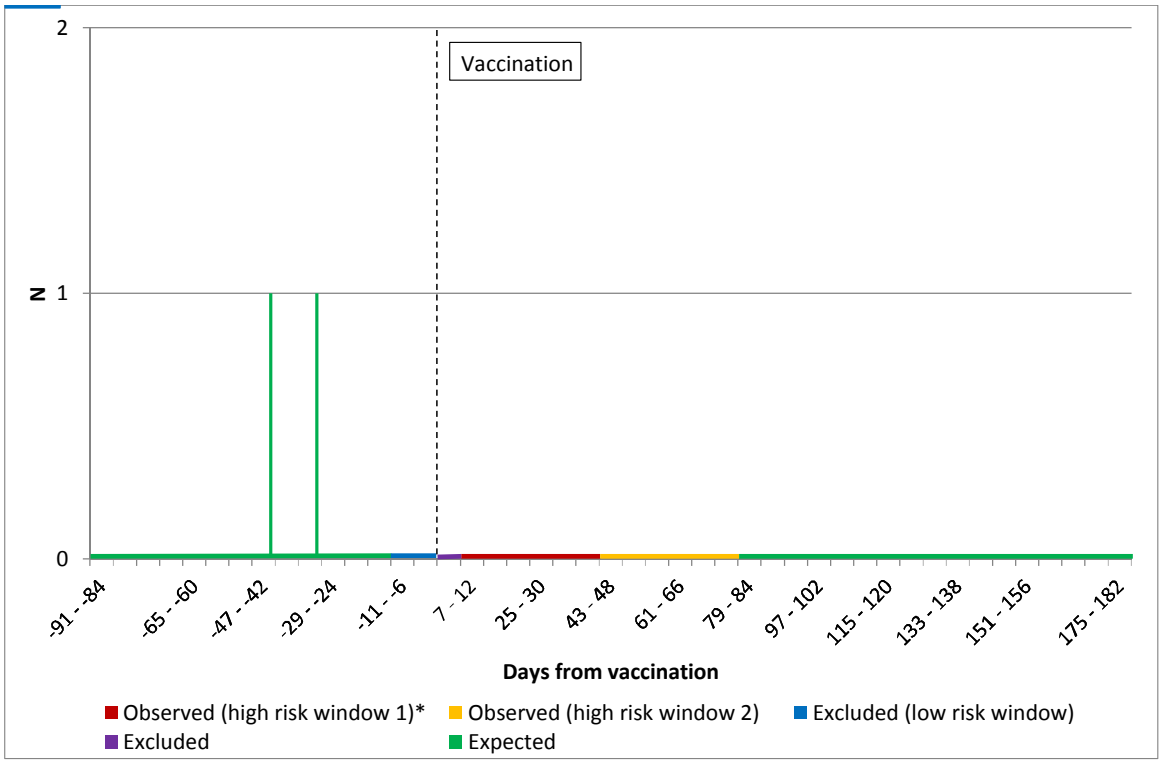



Uses the primary case definition. For explanation of the observed, excluded and expected time periods see Section 9.8.3 including Figure 2. Outcomes within each period are denoted by colour (see legend): high risk window 1 = days 0 – 7, high risk window 2 = days 8 to 30 and the excluded low risk window = days -14 to -1, where day 0 is the date of cTIV exposure (vaccination). The study period is spilt into 8 day periods except for the first window (-91 to -82 days) and the last window (171 to 182 days). 2 extra days are included in low risk grouping and 1 extra day is included in the second high risk window.



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**Figure B 3**: **Distribution of paraesthesia by time from cTIV exposure**

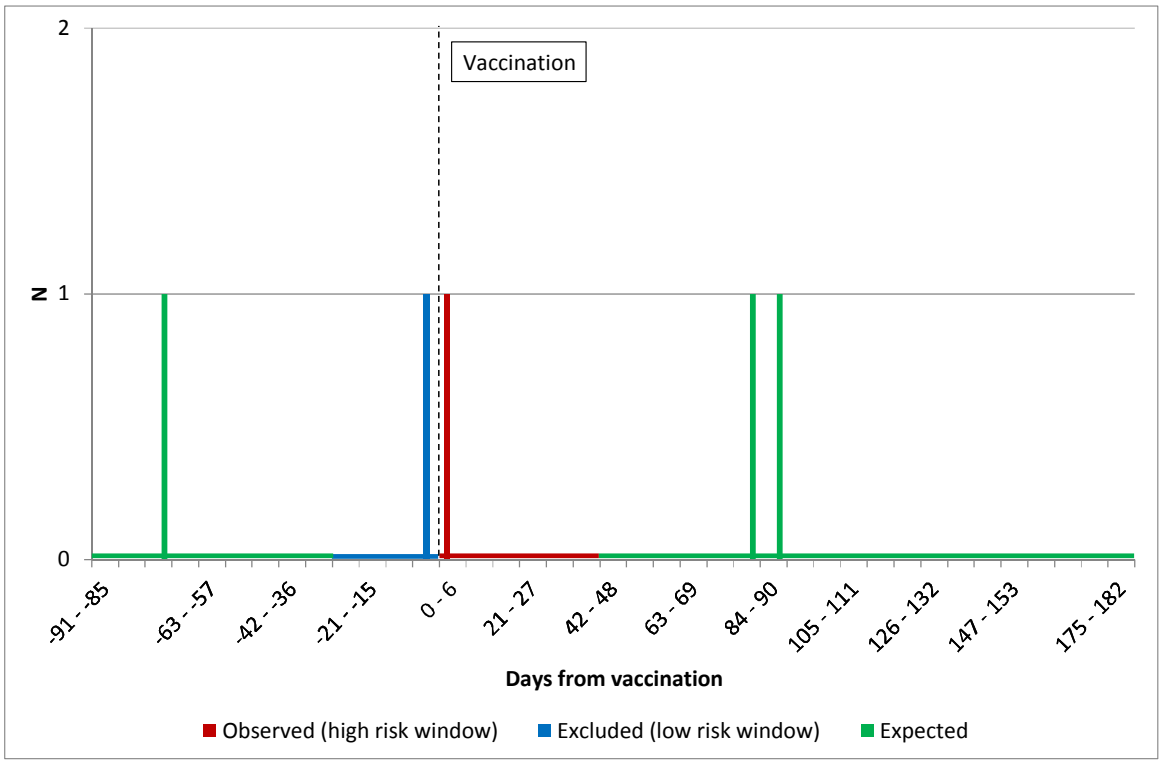



Uses the primary case definition. For explanation of the observed, excluded and expected time periods see Section 9.8.3 and Figure 2. Outcomes within each period are denoted by colour (see legend): High risk window 1 = days 7 to 42 and high risk window 2 = days 43 to day 77. The excluded low risk window is day -14 to day 0. Day 0 is the date of vaccination. Events in days 1-6 are not in an observed to expected analysis so this time is marked as excluded. The study period is spilt into 6 day periods except for the first window (-91 to -84 days), and the last widow (175 to 182 days 3 days of low risk window are excluded from low risk grouping and 1 extra day included in the second high risk window.



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**Figure B 4**: **Distribution of thrombocytopenia by time from cTIV exposure**

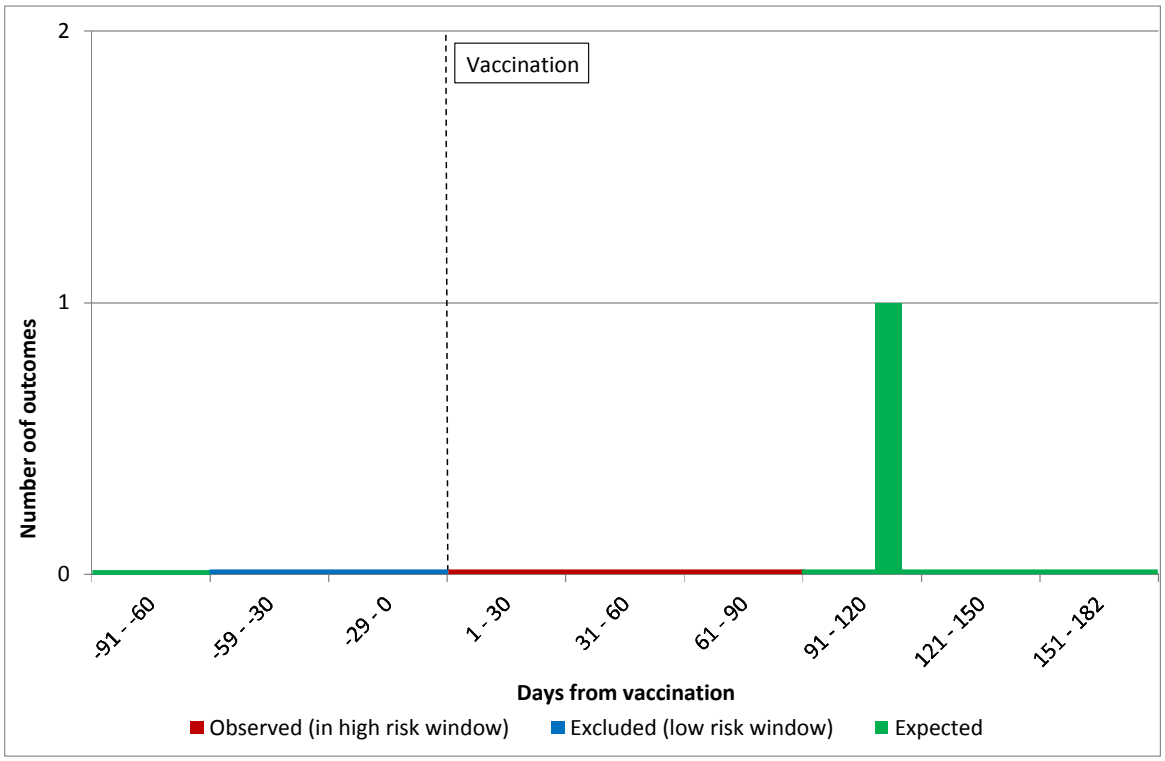



Uses the primary case definition. For explanation of the observed, excluded and expected time periods see Section 9.8.3 including Figure 2. Outcomes within each period are denoted by colour (see legend): the high risk window = days 0 to 42 and the excluded low risk window = days -30 to -1. Day 0 is the date of cTIV exposure (vaccination). The study period is spilt into 7 day periods except for the last widow (175 to 182 days). 1 day of high risk window is excluded from high risk grouping and 2 days of low risk window are excluded from low risk grouping.



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**Figure B 5**: **Distribution of Bell's palsy by time from cTIV exposure**

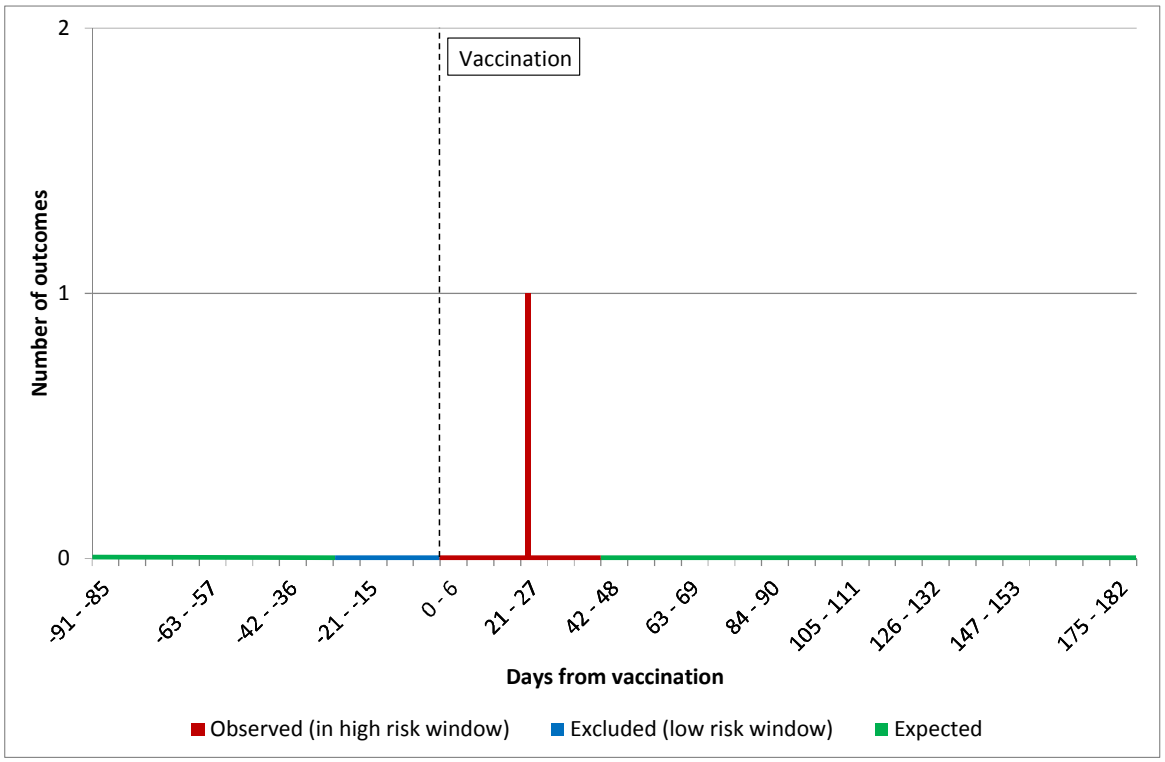



Uses the primary case definition. For explanation of the observed, excluded and expected time periods see Section 9.8.3 including Figure 2. Outcomes within each period are denoted by colour (see legend): Outcomes within each period are denoted by colour (see legend): the high risk window = days 1 to 90 and the low risk window = days -60 to 0. Day 0 is the date of cTIV exposure (vaccination). Study period is spilt into 30 day periods except for the first window (-91 to -60 days) and the last window (151 to 182 days) which both contain 32 days. 1 day of the low risk window is excluded from low risk grouping



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**Figure B 6**: **Distribution of IBD onset by time from cTIV exposure**

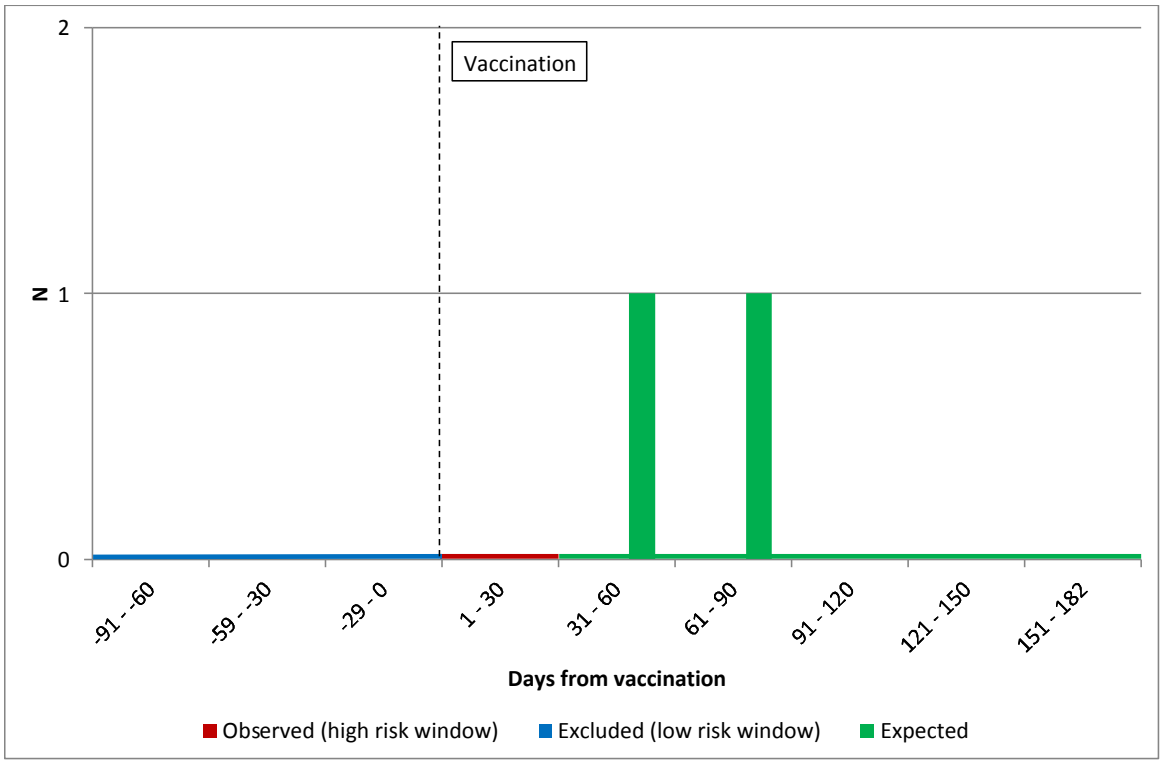



Uses the primary case definition. For explanation of the observed, excluded and expected time periods see Section 9.8.3 and Figure 2. Outcomes within each period are denoted by colour (see legend): high risk window = days 0 to 42 and the excluded low risk window = days -30 to -1. Day 0 is the date of cTIV exposure (vaccination). Study period is spilt into 7 day periods except for the last window (175 to 182 days) which contains 8 days. 2 days of low risk window are excluded from low risk grouping and 1 day of high risk window are excluded from high risk groupin



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**Figure B 7: Distribution of vasculitis onset by time from cTIV exposure**




Uses the primary case definition. For explanation of the observed, excluded and expected time periods see Section 9.9.2 Statistical Methods and Figure 2. Outcomes within each period are denoted by colour (see legend): high risk window = days 1 to 30 and the excluded low risk window = days -90 to 0. Day 0 is the date of cTIV exposure (vaccination). The study period is spilt into 30 day periods except for the first window (-91 to -60 days) and last window (151 to 182 days) which both contain 32 days. One extra day is included in the low risk.



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