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

The following guiding principles have been applied to the disclosure:

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

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

PASS information

Title	Risk of solid organ transplant rejection following vaccination with *Pandemrix* in the United Kingdom
Version identifier of the final study report	Study Report – Main – Final
Date of last version of the final study report	12 December 2013
EU PAS Register Number	Study not registered
Active substance	Purified antigen fractions of inactivated split virion Influenza A/California/7/2009 (H1N1)v-like strain
Medicinal product	Pandemrix™, Pandemic Influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted) A/California/7/2009 (H1N1)v like strain (X-179A)
Product reference	EU/1/08/452/001
Procedure number	EMEA/H/C/0832/
Marketing Authorisation Holder(s)	GlaxoSmithKline Biologicals
Joint PASS	No
Research question and objectives	To assess whether vaccination with *Pandemrix* (primary and secondary objectives) or with seasonal influenza vaccines (tertiary objective) is associated with an increased risk of solid organ transplant rejection of the liver, kidney, lung, heart, or pancreas. The results for the primary and secondary objectives are presented in this first main study report. The results for the tertiary objective will be provided in a second annex report to the main report.
Country(-ies) of study	United Kingdom

Authors	Coordinating author: • [redacted], Project Manager – Science Writing GSK contributors: • [redacted], Lead Epidemiologist, GSK Biologicals • [redacted], Epidemiologist, GSK Biologicals • [redacted], Project Statistician, GSK Biologicals • [redacted], Senior Analyst, Observational Data Analytics, GSK R&D • [redacted], Director, Influenza - Epidemiology, GSK Biologicals • [redacted], Lead Statistician, Senior Manager, Statistician Epidemiology, GSK Biologicals • [redacted], Manager - Epidemiological portfolio, GSK Biologicals • [redacted] - Observational Data Analytics, GSK Biologicals • [redacted] - Director, Observational Data Analytics, GSK R&D • [redacted] - Global Study Manager, GSK Biologicals • [redacted] - Therapeutic Area Head, Vaccine Clinical Safety and Pharmacovigilance (VCSP)

Marketing authorisation holder(s)

Marketing authorisation holder(s)	GlaxoSmithKline Biologicals Rue de l'Institut 89, 1330 Rixensart, Belgium
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1. ABSTRACT

Title

Risk of solid organ transplant rejection following vaccination with *Pandemrix* in the United Kingdom.

Keywords

H1N1 pandemic influenza, safety, transplantation, rejection, CPRD, HES, SCCS

Rationale and background

Influenza viruses can cause a spectrum of illness in transplant recipients with a high rate of lower respiratory disease. Solid organ transplant (SOT) recipients are a recommended priority group for pandemic and seasonal trivalent influenza vaccination (TIV) due to the elevated risk of complications associated with these infections. Safety data for pandemic H1N1 vaccination in this population are currently limited.

Research question and objectives

The aim was to assess whether vaccination with GSK's inactivated adjuvanted (AS03) A/H1N1 pandemic influenza vaccine *Pandemrix* (primary and secondary objectives) or TIV (tertiary objective) are associated with an increased risk of rejection of SOT (liver, kidney, lung, heart, or pancreas). Results for the primary and secondary objectives are presented in this first main study report; results for the tertiary objective will be provided in a second annex report.

Study design

Retrospective self-controlled case-series analysis.

Setting

The UK Clinical Practice Research Datalink General Practitioner OnLine database (CPRD GOLD) and its linked component of the Hospital Episodes Statistics (HES)

Subjects and study size

The overall study population included 184 solid organ transplant recipients, of which 71 subjects were exposed to *Pandemrix*.

Variables and data sources

Data sources consisted of the CPRD/GOLD, HES, and a standardised GP questionnaire. Endpoint for the primary and secondary objectives was the occurrence of at least one SOT rejection in the study period 01-October-2009 to 31-October-2010. The risk periods were one and two months after *Pandemrix*; the control periods corresponded to this study period excluding the risk period(s). Covariates in the multivariate models included time

since transplantation; TIV administration; previous rejection(s); bacterial infections; viral infections; malignancies/cancers; chemotherapy.

Results

Results of the main analysis indicate a relative incidence of SOT rejection of 1.05 (95% CI: 0.52 - 2.14) one month after vaccination. These estimates remained stable across several sensitivity and exploratory analyses. In the analysis subsets that incorporated subjects for which questionnaire information was available and valid, the range of risk estimates was similar. Analyses were mainly driven by kidney, the most commonly transplanted organ in the UK (RI = 0.85, 95% CI: 0.38 - 1.90).

Discussion

The study used data from HES, an appropriate source of information for this outcome typically managed in hospital settings. SOT rejection is a complex outcome, affected by several potential risk factors. The SCCS design implicitly controls for fixed confounders, however, except for time since transplantation, risk factors such as infections could not be fully accounted for. The consistent range of risk estimates all in the vicinity of 1.0, with upper 95% confidence limits around 2.0, suggest no evidence of an increased risk of SOT rejection following vaccination with *Pandemrix* in the UK. The results do not suggest a change in the benefit-risk profile of *Pandemrix*. This study provides important safety data to inform the benefit-risk of an ASO3-adjuvanted pandemic influenza vaccine in transplanted patients in the event of a future pandemic.

Marketing Authorisation Holder(s)

GlaxoSmithKline Biologicals, Rue de l’Institut 89, 1330 Rixensart, Belgium

Names and affiliations of principal investigators

Not applicable

2. LIST OF ABBREVIATIONS

CI	Confidence Interval
CPRD GOLD	Clinical Practice Research Datalink General Practitioner OnLine (database)
EMA	European Medicines Agency
EU	European Union
GP	General Practitioner
GSK	GlaxoSmithKline
HES	Hospital Episodes Statistics
ISAC	Independent Scientific Advisory Committee
LL	Lower limit
NHS	National Health Service
nvac	Not vaccinated
QC	Quality Control
RI	Relative Incidence
SCCS	Self-Controlled Case-Series
SD	Standard Deviation
SOT	Solid organ transplant
TIV	Trivalent Influenza vaccine
UK	United Kingdom
UL	Upper Limit
vac	Vaccinated
VCSP	Vaccine Clinical Safety and Pharmacovigilance

3. ETHICS

3.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The study protocol, the protocol amendment, and other information that required pre-approval were reviewed and approved by the Independent Scientific Advisory Committee (ISAC) of the Clinical Practice Research Datalink General Practitioner OnLine Database (CPRD GOLD).

3.2. Ethical conduct of the study

The study was conducted in accordance with all applicable regulatory requirements, with the Guidelines for Good Pharmacoepidemiology Practices (GPP) [ISPE, 2007], all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

3.3. Subject information and consent

No patient informed consent was needed, because the patient information in the CPRD GOLD is fully coded and GlaxoSmithKline (GSK) Biologicals personnel was not able to make a link between the data and specific individuals.

The CPRD GOLD has an ethical approval from a Multi-centre Research Ethics Committee for purely observational research (i.e. studies that do not include patient involvement [CPRD GOLD, 2013a]).

4. INVESTIGATORS

Not applicable.

5. OTHER RESPONSIBLE PARTIES

GSK Biologicals had the overall responsibility for the conduct of the study.

[redacted] was the GSK Biologicals designated Lead Epidemiologist for this study.

The ISAC of CPRD GOLD reviewed the protocol and other information requiring pre-approval. The key roles of this committee are to provide expert advice on the medical aspects, statistical/epidemiological aspects and methodological aspects of studies involving CPRD GOLD [CPRD GOLD, 2013b].

Study results were presented to the GSK Safety Review Team, who provides a central and dedicated forum for safety evaluation of emerging data that could impact subject safety.

6. MILESTONES

Milestone	Planned date	Actual date	Comments
Approval of protocol by ISAC	Not applicable	13-SEP-2012	Approval of the protocol
Registration in the EU PAS register	Not applicable	Not applicable	Protocol developed before the PASS regulation came into force
Start of data collection	31-AUG-2012	27-SEP-2012	General Practitioner (GP) questionnaires were sent out via CPRD on 31-OCT-2012
Submission of protocol amendment to ISAC	05-JUL-2013	05-JUL-2013	Reasons for protocol amendment explained in Section 9.
Approval of amendment	Not applicable	15-JUL-2013	None
Database freeze	13-SEP-2013	07-AUG-2013	End of data collection
Statistical analysis complete	31-OCT-2013	06-DEC-2013	None
Final report of Main study results – Primary and Secondary study objectives	13-DEC-2013	12-DEC-2013	None
Annex report to Main report – Tertiary study objectives	End of MAR-2014	Not applicable	None

7. RATIONALE AND BACKGROUND

During the 2009 H1N1 influenza pandemic, mass vaccination with GSK's inactivated adjuvanted (AS03) A/H1N1 pandemic influenza vaccines *Pandemrix* and Arepanrix™ was initiated in 47 countries worldwide, with large vaccine coverage and/or single use in several countries (e.g., Finland, Sweden, Canada). Between October 2009 and March 2010, more than 30 million doses were administered across the EU, where *Pandemrix* was the predominant vaccine used. According to data from the UK Department of Health based on the ImmForm national survey, *Pandemrix* was used widely and in the majority of target groups in the UK, with less than 0.1% of individuals having received vaccines from other manufacturers (mainly Celvapan®) [Department of Health, 2010].

After the pandemic, cases of solid organ transplant (SOT) rejection following vaccination with *Pandemrix* and *Arepanrix* were spontaneously reported in the EU and Canada, respectively. Published reports also described cases temporally associated with vaccination, in kidney and heart transplant recipients immunised with a GSK A/H1N1 pandemic influenza vaccine [Schaffer, 2011] and in one pancreas transplant recipient immunised with a non-GSK adjuvanted vaccine [Vistoli, 2011]. Other studies on the safety of pandemic vaccines (adjuvanted and non-adjuvanted; from GSK and from other manufacturers) in patients with lung, kidney, liver and heart transplants showed no events of acute rejection [Schuurmans, 2011; Duesberg, 2010; Hauser, 2011; Fairhead, 2011a; Fairhead, 2011b; Goldschmidt, 2011; Altamirano-Diaz, 2011; Torii, 2011; Crespo, 2011; Esposito, 2011; Vazquez-Alvarez, 2010]. All studies were descriptive and based on relatively small sample sizes. The association between vaccination and clinical rejection has been difficult to assess due to the multiple risk factors for rejection, including infections, co-morbidities, and lack of compliance with immunosuppressive treatments. A cohort study of 216 SOT recipients and 138 controls concluded that *Pandemrix* was safe in SOT recipients; the prospective nature of the study accounted for some of the difficulties of retrospectively collecting transplantation/rejection data as was done in the

majority of studies conducted after the pandemic [Siegrist, 2012]. The majority of published reports simultaneously evaluated antibody responses to the vaccines and safety. There was substantial heterogeneity between study populations with regards to: patient history (including time since transplantation), overall antibody response to the vaccines, selection criteria for vaccination, vaccination coverage, immune-suppressive drug regimen, case definition for rejection, selection criteria for biopsy, detection methods for anti-HLA antibodies, presence and adequacy of a control population, and information on background rates of observed events.

While data on the safety of pandemic vaccination in transplanted patients during the 2009 H1N1 pandemic remains relatively limited, it has been postulated that seasonal trivalent influenza vaccine (TIV) administration might increase the risk of SOT rejection. Although generally administered from 3-6 months post-transplantation [Kumar, 2011], once baseline immune-suppression levels are attained, little data is available on the appropriate timing for influenza immunisation following transplantation. On the other hand, influenza viruses cause a spectrum of illness in transplant recipients with a high rate of lower respiratory disease and have been associated with higher morbidity and mortality, graft rejection and prolonged viral shedding [Vilchez, 2002; Weinstock, 2003]. Although the efficacy of seasonal (and pandemic) influenza vaccination in SOT recipients remains controversial, influenza vaccination is an important public health measure recommended for transplant recipients, due to the substantially elevated risk of complications associated with influenza infection [KDIGO, 2009].

A recent review of published studies of the efficacy and safety of influenza vaccination (including pandemic) in SOT recipients concluded that there is no evidence from larger studies of an elevated risk of clinical rejection, and that influenza infection, rather than vaccination, is associated with a risk of allograft dysfunction. Despite some evidence linking influenza immunization to transiently increased measures of cellular alloreactivity, elevated rates of clinical rejection or allograft dysfunction are not generally observed in vaccinated patients [Avery, 2012]. Another review [Cordero and Manuel, 2012] came to similar conclusions, highlighting that influenza vaccination (including pandemic) is safe and well tolerated in transplanted patients, despite relatively low efficacy.

Considering that SOT recipients are a target group for influenza immunisation, it is important to inform the benefit-risk of ASO3-adjuvanted pandemic influenza vaccines in transplanted patients, in the event of a future pandemic. GSK committed to the European Medicine’s Agency (EMA) to further explore the SOT rejection signal and proposed a retrospective study in the Clinical Practice Research Datalink GP Online Database (CPRD GOLD). Given the complexity of the outcomes under study, the most appropriate design would have been a prospective study allowing standardised definitions for both the patient population and the outcomes. However, this design could not be considered given that pandemic vaccines were no longer being used; therefore, a retrospective observational study was conducted using a self-controlled case-series (SCCS) design, as requested by the EMA.

8. RESEARCH QUESTION AND OBJECTIVES

The study was intended to assess whether vaccination with *Pandemrix* (primary and secondary objectives) or with TIV (tertiary objective) was associated with an increased risk of solid organ transplant rejection of the liver, kidney, lung, heart, or pancreas.

8.1. Primary objective

- To assess the risk of SOT rejection (liver, kidney, lung, heart, pancreas) within one month after vaccination with *Pandemrix*.

8.2. Secondary objective

- To assess the risk of SOT rejection (liver, kidney, lung, heart, pancreas) within two months after vaccination with *Pandemrix*.

8.3. Tertiary objectives

- To assess the risk of SOT rejection (liver, kidney, lung, heart, pancreas) within one month after seasonal influenza vaccination, during influenza seasons 2006/2007, 2007/2008 and 2008/2009.
- To assess the risk of SOT rejection (liver, kidney, lung, heart, pancreas) within two months after seasonal influenza vaccination, during influenza seasons 2006/2007, 2007/2008 and 2008/2009.

9. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	15-July	Contributing authors; Data collection; Statistical methods; Appendix E: Algorithms and codes for data extraction; Appendix F: Examples of Tables	Amendment	For the primary analyses, the study team initially planned to use the information from the GP questionnaires (a subpopulation of identified subjects from CPRD-HES). Based on preliminary analysis of information obtained from the GPs, transplant rejection events appeared to be under-reported and under documented, with GPs reporting less than 40% of the number of rejections initially identified in CPRD/HES, possibly because transplant rejection is handled in specialty/hospital settings. Therefore, HES was considered a more reliable primary source of information for this specific outcome and used to carry out the primary analyses, while combined information from CPRD/HES and GP questionnaires was used to carry out analyses for the secondary analyses. See Section 3 of the attached Protocol Amendment for full details.

10. RESEARCH METHODS

10.1. Study design

This study was a post-authorisation safety study (PASS), addressing an EMA commitment.

This was a retrospective, observational study using the CPRD GOLD data source and Hospital Episode Statistics (HES) data source in the UK.

The self-controlled case-series (SCCS) method was used to assess the temporal association between rejection of solid organ transplant and vaccination.

The SCCS relies on the observation of individuals with the outcome of interest (cases) for both a risk period and control period(s). Since the SCCS analysis relies on case data only, these studies can be performed without the challenges associated with comparison group selection and confounding [Farrington, 1995]. An important feature of this design is that it controls implicitly [Whitaker, 2006] for potential confounders which do not vary with time (e.g. socio-economic status, gender). Additionally, fewer cases are usually required, as compared to a case-control design.

In the present study, the SCCS design required data on transplant rejection events and on cases' history of pandemic and trivalent influenza vaccination (TIV). The risk estimate was derived from a Poisson model by conditioning on the occurrence of rejection.

The overall study period ranged from 01 September 2006 through 31 October 2010. This period was divided as follows:

- Study period to assess the risk of SOT rejection following vaccination with *Pandemrix* (primary and secondary objectives): 01 October 2009 to 31 October 2010.
- Study period to assess the risk of SOT rejection following vaccination with TIV (tertiary objectives): 01 September 2006 to 31 August 2009.

The risk period in the primary objective was one month after vaccination with *Pandemrix*, and the risk period was two months in the secondary objective. The one-month risk period was based on the latency observed in spontaneous cases reported to GSK, and was agreed by the CHMP; it also corresponded to the most common period with higher risk of rejection following other exposures such as acute infection (Expert advice). The control period corresponded to the overall study period, excluding the risk period.

10.2. Setting

The study was conducted in the UK Clinical Practice Research Datalink General Practitioner OnLine database (CPRD GOLD) and its linked component of the Hospital Episodes Statistics (HES).

10.3. Subjects

Subjects enrolled in the study were solid organ transplant recipients with at least one episode of rejection of solid organ transplant between 01 September 2006 and 31 October 2010.

Cases were identified using a stepwise approach as described in the protocol (see Protocol Amendment Appendix A: Algorithms and codes for data extraction of the protocol).

Identification of cases in HES and CPRD GOLD

The outcome under study was rejection of at least one of the five transplanted organs (lung, kidney, heart, liver and, pancreas) during the study period. There was no age limitation. Patients had to be considered acceptable in the CPRD GOLD database. CPRD GOLD acceptable records are defined as patients with no breaks in their records, and information on their year of birth, first registration date, and sex [Williams, 2012].

The steps of identification of the study population were detailed in the protocol (Appendix A) and summarised in Figure 1. The study dataset was built using the latest CPRD release: 2012Q3 release of the CPRD GOLD available to GSK at the time of approval of this protocol.

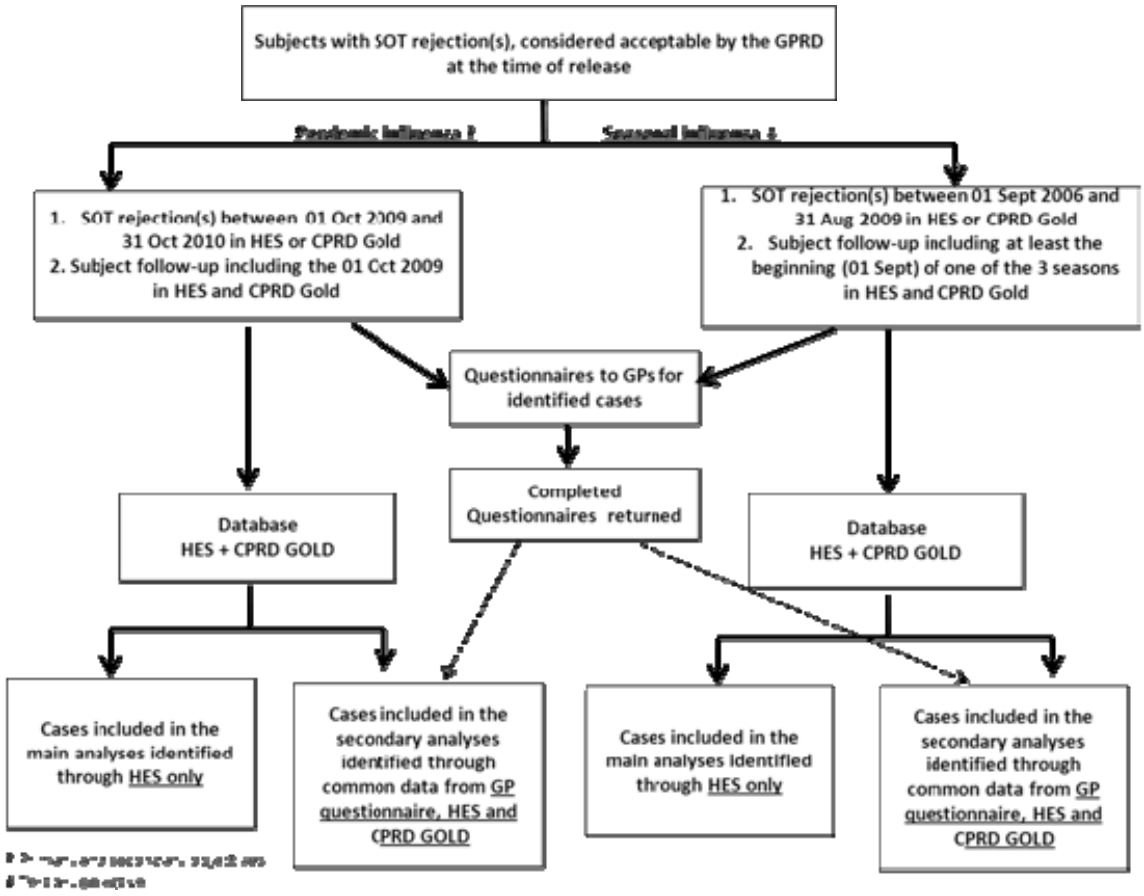
Inclusion criteria

- Subject defined as acceptable in the CPRD GOLD;
- Subject with at least one solid organ transplant rejection reported in the CPRD GOLD and/or HES during the study periods (01 September 2006 to 31 August 2009; 01 October 2009 to 31 October 2010).

Exclusion criteria

- Subject from HES (”hesid”) matched to more than one subject in the CPRD GOLD (“patid”).

Figure 1 Identification of the study population



10.4. Variables

- The endpoint for the primary and secondary objectives was the occurrence of SOT rejection within the period from 01 October 2009 to 31 October 2010.
- The endpoint for the tertiary objective was the occurrence of SOT rejection within the period from 01 September 2006 to 31 August 2009.

Two data sources were used: CPRD/HES (primary data source) and CPRD/HES and the GP questionnaire (secondary data source). The variables were defined using the algorithms presented in the protocol (see Appendix A of the Protocol Amendment). All codes used in this study were reviewed by a physician. Outcome variables were also obtained from GP questionnaires.

10.5. Data sources and measurement

10.5.1. The CPRD GOLD

The CPRD GOLD is the world's largest computerised database of linked anonymised longitudinal medical records from primary care. The data are drawn from the computer systems used by general practitioners to maintain the clinical records within their practices. As of March 2011, CPRD GOLD contained records from over 12 million patients contributing 64 million person-years of prospectively recorded high-quality primary healthcare data [Williams, 2012].

The CPRD GOLD contains coded longitudinal medical records from general practices (i.e., records of clinical events [medical diagnoses], referrals to specialists and secondary care settings, prescriptions issued in primary care, records of immunisations/vaccinations, diagnostic testing, lifestyle information [smoking and alcohol status] and all other types of care administered as part of routine general practitioner [GP] practice), and more recently certain key data from hospital-based care (Hospital Episode Statistics) [CPRD GOLD, 2013c].

The CPRD GOLD data release of Q3 2012 contained data for 10,547,532 research standard patients, drawn from 644 practices throughout the UK. A total of 4,621,799 patients from 546 practices were active in the database. The CPRD GOLD population structure closely matches the age and gender distribution of the UK population as a whole. Mean database follow-up is 6.8 years (median 5.0 years). Recorded data include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and their major outcomes. Data are retrieved by means of the READ classification system; READ codes are a coded thesaurus of clinical terms, which are the basic means by which clinicians record patient findings and procedures in health and social care IT systems across primary and secondary care (e.g. GP surgeries and pathology reporting of results). The medcodes are the abbreviated terms which mean CPRD GOLD medical codes. Medcodes consisting of READ codes are used to enter medical diagnosis in the CPRD GOLD database.

The large majority of transplanted patients were predicted to be followed in hospital settings. General Practitioners (GP)s are routinely informed of rejection events via discharge letters from hospital departments and specialty care, however, it could be expected that a proportion of events are not encoded by the GPs and thus could be identified via the linkage between the CPRD GOLD and HES.

10.5.2. The Hospital Episode Statistics (HES)

Hospital Episodes Statistics (HES) is the data source that collates information about all health care provided by National Health Service (NHS) hospitals in England. The records include more than 125 million admitted patient, outpatient and accident and emergency records each year [Hospital Episode Statistics, 2013; Sinha, 2012]. Discharge diagnoses are classified using ICD-10 terminology.

The HES database contains details of all admissions to National Health Service (NHS) hospitals in England; patients registered in 56% of all GP practices contributing to the CPRD GOLD are linked to the HES database. Not all patients in the CPRD GOLD have linked data (e.g. if they live outside England or if their GP does not agree that their data should be used). HES data linkage are limited to CPRD GOLD research-standard patients. CPRD GOLD records are linked to the HES by a trusted third party using a combination of the patient's NHS number, gender, date of birth and postcode.

10.5.3. The GP questionnaire

For all cases of solid organ transplant rejection, a standard questionnaire was sent to the GPs via the CPRD GOLD Research Group. Based on the inclusion/exclusion criteria and rules described in the protocol (see Algorithms in Appendix A of the protocol), data was extracted that would allow the identification of transplanted patients that experienced at least one rejection in the overall study period (2006-2010). A list of Patient IDs, together with the corresponding GP Practice IDs, was provided to the CPRD. The CPRD was in turn required to send the identified GP the questionnaire, with guidelines for completion in an attached information sheet. Filled questionnaires returned by the GPs were anonymised and information sent to the study Principal Investigator as described in the protocol (See Appendix B of the protocol – GP questionnaire).

For a given subject, GPs were asked:

- To confirm transplantation status and indicate the date of transplantation;
- To provide information on history of rejections including date and type of rejection;
- To report their patient's compliance with treatment before rejection;
- To report information on selected cofactors (e.g., influenza infection, influenza-like illness, opportunistic infections, duration of chemotherapy if applicable).

10.6. Bias

Potential bias and confounding in the study results were considered a priori to inform decision on which covariates to include in the statistical models. These covariates include risk factors for transplant rejection independent from H1N1 influenza vaccination, such as time since transplantation, TIV administration; various bacterial and viral infectious agents; previous rejection(s); cancer and chemotherapy (see Section 10.8.1.2). To account for potential bias, the following steps were taken:

- Use of HES/CPRD GOLD as the primary data source because of lack of consistency with HES data / lack of completeness of information in the GP questionnaires.
- For some rejections, the organ was not specified, thus the organ type was imputed according to the algorithm described in the protocol (see Protocol Amendment: Appendix A - Algorithms and codes for data extraction).

Subjects with multiple transplantations could present a very specific risk profile. However, their number was expected to be limited and it was not deemed necessary to exclude these subjects from the inferential analyses.

Pandemrix vaccination was not evenly distributed across the study period (i.e. the vaccination campaign was mainly limited to the winter season). In this situation, the results of the SCCS analyses could be biased if the baseline risk of SOT rejections is also unevenly distributed during the pandemic study period. In such a scenario, the relative incidence of SOT rejection after *Pandemrix* vaccination would be underestimated if the baseline risk of rejection is lower during the vaccination period, or overestimated in case the baseline risk of rejection is higher.

10.7. Study size

Sample size was estimated using the following information and assumptions defined based on feasibility data for the incidence of SOT rejection in the former General Practice Research Database (GPRD) in 9,166 transplanted patients (see the protocol - Appendix C– Feasibility assessment):

- Distribution of transplantation dates (liver, kidney, heart, lung or pancreas) based on GPRD data until 24-Jun-2011;
- Distribution of the first and second doses of *Pandemrix* based on the Post-Authorization Safety Study (PASS) of *Pandemrix* conducted by GSK in the UK general population (N=9,143 subjects) [Nazareth, 2013] ;
- Baseline incidence (>90 days post-transplantation) of transplant rejection (liver, kidney, heart, lung or pancreas): 13.14 cases per 1,000 patient-years;
- Effect of time since transplantation: true RI between first 31 days (day0-day30) post-transplantation and the baseline incidence: 6.22, and between the period from day 31 to day 90 and baseline: 3.09;
- Post-vaccination follow-up period: 181 days. Two risk periods were defined: 31 days (primary objective) and 61 days (secondary objective) after any dose. Control periods: 150 and 120 days, respectively;
- Proportion of subjects who received two doses: 0% or 45%;
- True RI between the risk and control periods: 1, 2, 3, 4 and 5;
- Number of cases: 10, 15, 20, 30 and 40.

For each scenario 1,000 simulations were performed using SAS 9.2. On the basis of the evolution of the incidence of rejection after transplantation, three post-transplantation periods were defined: 0-30, 31-90 and more than 90 days.

Considering that 45% of the transplanted subjects received two doses, and a risk period of 31 days post vaccination (any dose):

- With 10 cases, there was 70% power to detect a RI of 5 or higher;
- With 20 cases, there was 85% power to detect a RI of 4 or higher;
- With 30 cases, there was 80% power to detect a RI of 3 or higher;
- With 40 cases, there was 52% power to detect a RI of 2 or higher.

Based on these power simulations, it was decided to not conduct any formal analysis if the final number of exposed cases would be below 10 and limit the analyses to descriptive information (e.g. demographics; patient history related to transplantation including rejection; type of organ transplanted; dates of transplantation, H1N1 immunisation, and rejection event following immunisation; immune-suppressive drug regimen; co-morbidities including infections).

10.8. Data transformation

10.8.1. Subject follow-up

For each subject, the follow-up was defined separately for each season. The beginning of the follow-up was 01 October 2009 for the pandemic season, and 01 September of each season for the other influenza seasons (i.e., 2006/2007, 2007/2008, 2008/2009). The end of follow-up corresponded to whichever of the following dates/events comes first:

- 31 October 2010 for the pandemic study period; 31 August 2007, 2008, or 2009 for the seasonal influenza study periods;
- A new transplantation event as defined in the protocol (see Appendix A of the protocol);
- Subject death;
- Last collection date of the GP practice the subject was registered with;
- Transfer out date of the subject: the subject was included up to the “transfer out date”, in order to ensure continuous follow-up during a given season.
- Last date of collection of HES data in the CPRD-GOLD release used for the analyses.

10.8.1.1. Subsets of the study population

Four subsets of cases were to be defined for the analyses (see Figure 2).

Pandemic influenza study period (01 October 2009 – 31 October 2010):

Subset 1a. The primary pandemic influenza subset was to include subjects:

- with a follow-up in the CPRD GOLD and in HES during the pandemic season including 01 October 2009 and the preceding 180 days period (from 04 April 2009),

AND

- with at least one rejection reported in HES, within the subject followed-up for the pandemic season.

Subset 1b. The secondary pandemic influenza subset was to include subjects:

- with a follow-up in the CPRD GOLD and in HES during the pandemic season including 01 October 2009 and the preceding 180 days period (from 04 April 2009), AND
- with a GP questionnaire returned and with all required information available after review based on a quality check of data,

AND

- with at least one rejection reported in HES, in the CPRD GOLD or in the GP questionnaire, within the subject followed-up for the pandemic season.

Seasonal influenza study period (01 September 2006 – 31 August 2009):

Subset 2a. The primary seasonal influenza subset was to include subjects:

- with a follow-up during at least one of the influenza seasons (2006/2007, 2007/2008 or 2008/2009) in the CPRD GOLD and in HES. The subject follow-up must have included:
- 01 September and the preceding 180 days period (from 05 March) in the CPRD GOLD and in HES,

AND

- at least one rejection reported in HES in at least one of the 3 influenza seasons.

Subset 2b. The secondary seasonal influenza subset was to include subjects:

- with a completed GP questionnaire returned and containing all information needed for the analyses,

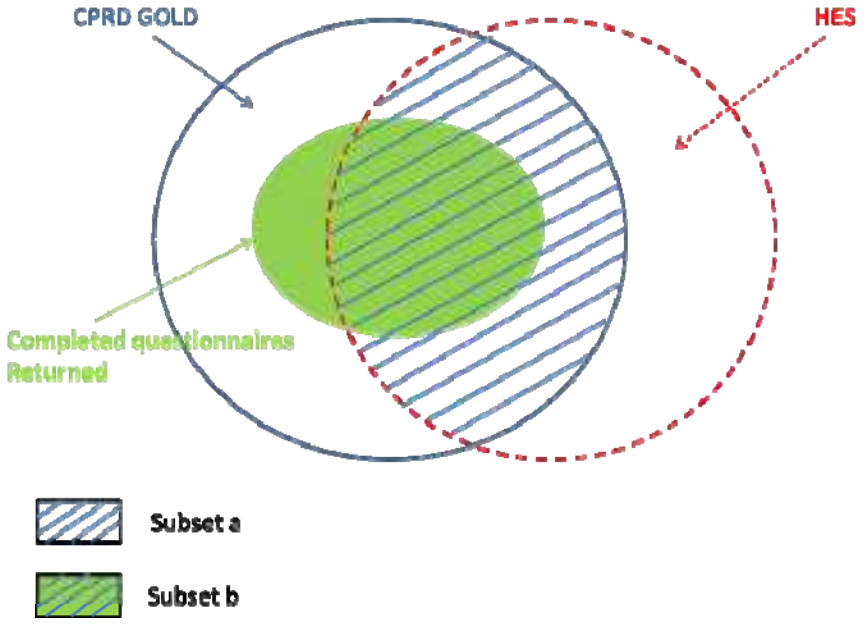
AND

- with a follow-up during at least one of the influenza seasons (2006/2007, 2007/2008 or 2008/2009) in the CPRD GOLD and in HES. The subject follow-up must have included:
  - 01 September and the preceding 180 days period (from 05 March) in the CPRD GOLD and in HES,

  AND

  - at least one rejection reported in HES, or in the CPRD GOLD or in the GP questionnaire, in at least one of the 3 influenza seasons.

Figure 2 Data source for case selection for subsets a and subsets b



10.8.1.2. Covariates

The approach used to identify the covariates included in the analyses was detailed in the protocol (see Appendix A of the protocol).

Pandemrix vaccination: A risk period of 31 days (day 0-30) or 61 days (day 0-60) (primary and secondary objectives, respectively) was associated with each dose. Vaccination information was extracted from the CPRD GOLD.

Time since transplantation: The period following any transplantation was divided into four periods corresponding to different risk periods: day 0-30, 31-90, 91-180 and >180. The category >180 days corresponded to the control period in the analyses. The detailed approach to detect the events was provided in the protocol (see Appendix A of the protocol). For the primary analyses only data from CPRD GOLD and HES was considered. For the secondary analyses additional information related to transplantations reported in the GP questionnaires was also taken into consideration.

Seasonal influenza vaccination: A risk period of 31 days (day0-30) or 61 days (day 0-60) was associated with each dose. Vaccination information was extracted from the CPRD GOLD.

Respiratory, opportunistic and acute bacterial infections: A risk period of 31 days (day0-30) was associated with each occurrence of infection from any data source (CPRD GOLD or GP questionnaire).

Chronic viral infection: A risk period of 366 days (day0-365) was associated with each occurrence of infection in the CPRD GOLD.

Malignancy/cancer: A risk period of 366 days (day0-365) was associated with each occurrence of malignancy/cancer in the CPRD GOLD.

Chemotherapy: If duration of chemotherapy was reported in the GP questionnaire, the associated risk period was to start at the date of chemotherapy initiation and end 365 days post-therapy.

Previous rejection - temporal effect: If one or more rejection episode(s) occurred within 180 days before the beginning of the study period of interest (01 October 2009 for the pandemic season, and 01 September of each other influenza seasons), a risk period of 181 days (day0-180) was associated with the last episode. Day 0 of the risk period was the date of rejection (as defined in the protocol: Appendix A).

If the risk periods of several events of the same covariate were overlapping, a combined risk period would span from the start date of the first event to the end date of the last event.

For all covariates except time since transplantation, if the risk periods of several events of the same covariate were overlapping, a combined risk period would span from the start date of the first event to the end date of the last event. For time since transplantation, the risk periods associated with the most recent transplantation would be considered.

10.9. Statistical methods

10.9.1. Main summary measures

The effect of the vaccination on the risk of SOT rejection is expressed as the relative incidence (RI) for the post-vaccination risk periods. The RI is calculated as the incidence rate of SOT rejection occurring in the pre-defined post-vaccination risk period as compared to the incidence rate of events observed in the control period.

10.9.2. Main statistical methods

10.9.2.1. Hypothesis

Null hypothesis (H0): the incidence rate of solid organ transplant rejection in exposed subjects is the same during the risk period and the control period.

Alternative hypothesis (H1): the incidence rate of solid organ transplant rejection in exposed subjects is different during the risk period and during the control period.

10.9.2.2. Descriptive Statistics

Frequency tables were generated for categorical variables. Mean, median, standard deviation, minimum, maximum were provided for continuous data such as age.

The following characteristics were analysed:

- Disposition of the study population;
- Distribution of subjects and person-time in each influenza season, for each population subset;
- Description of influenza vaccine exposure (0, 1, 2 doses) for each season, and for each population subset;
- Age and time since transplantation at the beginning of each season, gender, region of GP practice the subject is registered with, number of transplantations during each season, number of rejections within 180 days before the beginning of each season, reasons for end of follow-up (e.g. death, new transplantation, end of study period), and infections/chronic conditions during each season (i.e., respiratory infection, acute bacterial infection, chronic viral infection, opportunistic infection, malignancies/cancers, chemotherapy) for each population subset and overall. For subsets 1a and 2a the data from the GP questionnaires were not considered.

10.9.2.3. Statistical Analyses – Primary objective

The association between SOT rejection and influenza vaccination (*Pandemrix* or TIV administration) was assessed by calculating the relative incidence (RI), which is the ratio of the incidence rate of SOT rejection during the risk period to the incidence rate during the control period, with associated 95% confidence intervals (CI). A single vaccine effect was estimated for all doses of a given vaccine (*Pandemrix* or TIV).

The most important restriction of the SCCS method is the requirement that the occurrence of an event should not change the probability of subsequent exposure [Whitaker, 2006]. In the PASS of *Pandemrix* conducted by GSK in the UK, approximately 50% of immuno-compromised individuals received 2 doses [GlaxoSmithKline, 2011]; thus, this restriction potentially applies to the present study, as it is likely that the occurrence of a rejection after the first dose of *Pandemrix* would result in the second dose not being administered. Therefore, the case-series analysis for perturbed post-event exposure was used and the 95% CI was estimated with the bootstrap method [Farrington, 2009]. The authors developed a model that relaxes the assumption of independence between occurrence of events and subsequent exposures, using a counterfactual modelling approach. The method is based on counterfactuals in which the occurrence of the event precludes future exposures – i.e. a patient experiencing a transplant rejection after the first dose of the vaccine would not receive the second dose. The estimating equations were established sequentially, starting from the second dose and working back through the first dose, deriving new estimating equations at each stage. The effect of each dose was analysed only in subjects with a rejection event occurring after the considered dose. Where a second dose was administered, the case-series score equations for the first dose were adjusted using an estimator derived from the equations

computerised for the second dose. Thus, a set of unbiased estimates was obtained using an iterative procedure.

The standard SCCS method was used in some sensitivity analyses [Farrington, 1995].

10.9.2.3.1. Primary objective

The one-month risk period was defined as 31 days (day 0 to day 30) after each dose of *Pandemrix* and the control period corresponded to the subject follow-up during the season 2009/2010, excluding the risk period.

The primary analysis was based on Subset 1a (primary pandemic influenza subset). Only rejection events reported in the HES were taken into account. The approach to identify rejection(s) was detailed in the protocol (protocol: Appendix A). Only the first rejection after 1 October 2009 was considered. If several rejections occurred during the follow-up, the subject was censored at the second rejection.

Primary analysis for the primary objective:

- Number of rejections and person-time in each risk and control period associated with *Pandemrix* vaccination: control before vaccination, risk after dose1, control after dose1, risk after dose2, control after dose2, etc.
- RI estimates associated with *Pandemrix* vaccination (all doses pooled) adjusted for time since transplantation.
- RI estimates associated with *Pandemrix* vaccination adjusted for time since transplantation and TIV administration.
- RI estimates associated with *Pandemrix* vaccination adjusted for time since transplantation and for each infection/chronic condition and malignancy/cancer in separate models.
- RI estimates associated with *Pandemrix* vaccination adjusted for time since transplantation, for TIV administration and for all infections/ chronic conditions and malignancy/cancer.

Secondary analyses for the primary objective:

All the above analyses were repeated for Subset 1b (secondary pandemic influenza subset). Data from the CPRD GOLD/HES and from the GP questionnaires were considered. In addition to the adjustment for time since transplantation and for each infection/ chronic condition and malignancy/cancer, RI estimates were adjusted for chemotherapy. The approach to identify the rejections was described in the protocol (see Protocol Amendment: Appendix A).

Exploratory analyses for the primary objective:

A previous rejection might influence the risk of a subsequent rejection. Although this effect was partially controlled in the case-series design if it was considered constant during the study period, it could modify the effect of vaccination, or could be time-dependent. Thus, the effect of previous rejection(s) on the risk of subsequent rejection(s) was investigated through the following sequential analyses:

The potential modifying effect of a previous rejection was planned to be tested by introducing an interaction term between the fixed effect of a previous rejection and the time-varying effect of vaccination in the model.

Number of cases allowing, a stratified analysis was to be conducted:

- Subjects with no rejection episodes before the beginning of the pandemic influenza season, or with rejection episode(s) that occurred >180 days before the beginning of the pandemic influenza season. RI estimate associated with vaccination adjusted for time since transplantation.
- Subjects with at least one rejection episode during the 180-day period prior to the pandemic influenza season. RI estimate associated with vaccination adjusted for time since transplantation and adjusted for the risk period associated with previous rejections.

These exploratory analyses were based on Subset 1a (primary pandemic influenza subset). Data from the CPRD GOLD and HES were used.

Planned analyses were conducted pooling all organs. In addition, despite limited statistical power associated with the analyses based on 10 exposed cases, additional analyses by organ were to be conducted only if a minimum of 10 rejections were observed for a given organ.

10.9.2.4. Statistical Analyses – Secondary objective

The same analyses described for the primary objective were performed, using a risk period of two-months, defined as 61 days (Day 0 to Day 60), after any dose of *Pandemrix*.

10.9.2.5. Statistical Analyses – Tertiary objectives

Assuming that rejection events are not independent across the three seasons, data from influenza seasons 2006/2007, 2007/2008 and 2008/2009 were analysed separately. However, additional analyses were also carried out combining all seasons.

For each season, only subjects with follow-up starting at least 180 days before 01 September were considered for the analyses. The risk periods were to span from day 0 to day 30, or from day 0 to day 60, after each TIV administration; the control period corresponded to any period of the follow-up, excluding the risk period.

The primary analysis was based on Subset 2a (primary seasonal influenza subset). Only rejection events reported in the HES were taken into account. The approach to identify rejection(s) was detailed in the protocol (see protocol: Appendix A). Only the first rejection after 01 September was to be considered. If several rejections occur during the follow-up, the subject was to be censored at the second rejection.

For the analyses of pooled seasons, the beginning of the study period for each individual was 01 September of the first season with 180 days available in HES before 01 September.

Primary analyses for the tertiary objectives:

- Number of cases and person-time in the risk period and control periods;
- RI estimates associated with TIV administration adjusted for time since transplantation;
- RI estimates associated with TIV administration adjusted for time since transplantation and for each infection/chronic condition and malignancy/cancer in separate models;
- RI estimates associated with TIV administration adjusted for time since transplantation and for all infections/ chronic conditions and malignancy/cancer.

Secondary analyses for the tertiary objectives:

All the above analyses for separate seasons were repeated for Subset 2b (secondary seasonal influenza subset). Data from the CPRD GOLD/HES and from the GP questionnaires were considered. In addition to the adjustment for time since transplantation and for each infection/ chronic condition and malignancy/cancer, RI estimates were adjusted for chemotherapy. The approach to identify the rejections was described in the protocol (see protocol: Appendix A). If more than 5% of the rejections were reported in the GP questionnaire to be chronic or of unknown type, a sensitivity analysis excluding these rejections was to be performed.

Exploratory analyses for the tertiary objectives:

The potential modifying effect of a previous rejection was tested for each season, and pooled seasons by introducing an interaction term between the fixed effect of a previous rejection and the time-varying effect of TIV administration in the model. The fixed effect was a binary variable: at least one rejection during the 180-day period before the beginning of the influenza season, or no rejection during this period. The interaction was tested in the model with adjustment for time since transplantation.

Stratified analyses (number of cases allowing):

- Subjects with no rejection episode before the beginning of the influenza season, or with rejection episode(s) that occurred >180 days before the beginning of the influenza season. RI estimate associated with vaccination adjusted for time since transplantation.
- Subjects with at least one rejection episode during the 180-day period prior to the influenza season. RI estimate associated with vaccination adjusted for time since transplantation and adjusted for the risk period associated with previous rejections.

These analyses were based on Subset 2a (primary seasonal influenza subset). Only the first rejection reported in HES was considered and subjects were censored at any subsequent rejection.

Planned analyses were conducted pooling all organs. In addition, despite limited statistical power associated with the analyses based on 10 exposed cases, additional analyses by organ were to be conducted only if a minimum of 10 rejections were observed for a given organ.

Results of the tertiary objectives will be described in the Annex report to the main report.

10.9.2.6. Statistical models

The models used in SCCS analyses were based on Poisson regressions (see [Farrington, 1995; Farrington, 2009] for details of the adjustment methods). For all models, the dependent variable was the number of cases of SOT rejection of all organs and, when applicable, the number of cases of SOT rejection of each organ, separately. All models were to include the total person-time during each period as an offset. Each model is described below with the list of independent variables.

Pandemic influenza study period

Model1: Vaccination with *Pandemrix*, Time since transplantation

Model2: Model1 with vaccination with TIV

Model3: Model1 with respiratory infection(s)

Model4: Model1 with acute bacterial infection(s)

Model5: Model1 with opportunistic infection(s)

Model6: Model1 with chronic viral infection(s)

Model7: Model1 with malignancy(ies)/cancer(s), chemotherapy

Model8: Model2 with respiratory infection(s), acute bacterial infection(s), opportunistic infection(s), chronic viral infection(s), malignancy(ies)/cancer(s), chemotherapy.

Model9: Model1 with interaction between vaccination with *Pandemrix* and fixed effect of previous rejection(s)

Model10: Model1 with temporal effect of previous rejection(s)

Seasonal influenza study period

Model11: Vaccination with TIV, Time since transplantation

Model12: Model11 with respiratory infection(s)

Model13: Model11 with acute bacterial infection(s)

Model14: Model11 with opportunistic infection(s)

Model15: Model11 with chronic viral infection(s)

Model16: Model11 with malignancy(ies)/cancer(s), chemotherapy

Model17: Model11 with respiratory infection(s), acute bacterial infection(s), opportunistic infection(s), chronic viral infection(s) and malignancy(ies)/cancer(s), chemotherapy.

Model18: Model11 with interaction between vaccination with TIV and fixed effect of previous rejection(s)

Model19: Model1 with temporal effect of previous rejection(s)

10.9.3. Missing values

The primary analyses were based on data from the CPRD GOLD and HES. As for any study using large healthcare databases, it cannot be excluded that some information is not recorded in the database. Questionnaires were sent to GPs to attempt to complement the data from the CPRD GOLD and HES. However, based on the information obtained from the GPs, transplant rejection events appeared to be under-documented by GPs. Therefore, HES was used as the primary source of information to carry out the primary analyses and combined information from HES / CPRD GOLD and questionnaires was used to carry out analyses for the secondary analyses.

10.9.4. Sensitivity analyses

Sensitivity analyses for the primary objective:

– RI estimates associated with *Pandemrix* vaccination (all doses pooled) adjusted for time since transplantation using the standard SCCS method [Farrington, 1995]. All rejection events (first and subsequent) were considered.

Sensitivity analyses for the tertiary objectives:

– RI estimates associated with the TIV administration exposure adjusted for time since transplantation using the standard SCCS method [Farrington, 1995]. All rejection events (first and subsequent) were considered.

10.9.5. Amendments to the statistical analysis plan

The following analyses were added to the analyses planned in the protocol:

- The self-controlled case-series models were not fitted if there were less than 10 subjects exposed to *Pandemrix*, or less than 5 subjects exposed for each of the covariates.
- Exploratory analyses planned only for subset 1a were also performed for subset 1b.

10.10. Quality control

The final study dataset was archived and stored on a secured, access limited, computer platform SAS Drug Development (SDD) according to GSK Biological Standard Procedures. Specific statistical programs were written in SAS 9.2 (or higher) and validated according to the GSK standard procedures. The validation of the quality control (QC) of the statistical analysis was documented. All statistical programs, output files and QC documentation were saved as read-only files on SDD.

The final study protocol, the protocol amendment, the final statistical report and the QC document, the main study report and the annex study report were to be archived on a Document management system based on the Documentum platform: Computer Aided Regulatory Submission.

11. RESULTS

This study has been designed to assess the risk of SOT rejection following vaccination with *Pandemrix*. To address this question, two risk periods were defined (one month and two months) and two analytical subsets were created (Subset 1a and subset 1b, see Section 10.8.1.1).

In addition, a tertiary objective was defined to assess the risk of SOT rejection following TIV administration, using also two analytical subsets (Subset 2a and Subset 2b, see Section 10.8.1.1).

Subsets 1a and 2a are based on data from CPRD/HES, whereas subsets 2a and 2b are based on data from CPRD/HES and from the GP questionnaire.

The present report describes the results for the primary pandemic influenza subset (Subset 1a; see Section 10.8.1.1) and secondary pandemic influenza subset (Subset 1b; see Section 10.8.1.1). A second annex study report will present results for the tertiary study objectives (see Section 8.3) involving the primary seasonal influenza subset (Subset 2a; see Section 10.8.1.1) and the secondary seasonal influenza subset (Subset 2b; see Section 10.8.1.1).

11.1. Participants

The total number of subjects with a SOT rejection identifier in the overall study period (2006-2010) in either CPRD GOLD and/or HES was 587 subjects and the majority of these subjects (545 subjects; 92.8%) had a HES link (Table 1).

With regards to the pandemic component of the analysis, the primary pandemic influenza subset (Subset 1a; see Section 10.8.1.1) contained 184 eligible subjects (31.4% of all 587 subjects identified; Table 1). The secondary pandemic influenza subset (Subset 1b; see Section 10.8.1.1), which was further restricted to subjects with returned GP questionnaires that had valid/usable information, contained 67 subjects (11.4%).

Details of the response rate for the GP questionnaires are provided below:

- From the 587 identified cases in CPRD GOLD or HES for the overall study period (2006-2010), 502 (85.5%) questionnaires were sent to the GPs; the remaining 85 subjects belonged to practices that were no longer active in the CPRD.
- From the 502 questionnaires sent, 359 (71.5%) were returned by the GPs.
- From the 359 returned questionnaires, 172 subjects (47.9%) were eligible for inclusion, i.e. subjects for whom the GPs addressed the question regarding occurrence of rejection (see Protocol Amendment Appendix B: GP questionnaire). Of these 172, 161 had a HES link (Table 1).
- For 67 subjects, there was a follow-up in CPRD GOLD and/or HES for the pandemic season 2009-2010 and at least one SOT rejection in either the CPRD GOLD, HES or the GP questionnaire between 01-Oct-2009 and 31-Oct-2010 (subset 1b).

11.2. Descriptive data

Person-years of follow-up in the study are described in Table 2 and Table 3, by season and by subset; the majority of subjects were followed for the whole duration of the seasons, and this applied to all four subsets. For the primary pandemic influenza subset, the majority of subjects (179/184 subjects; Table 16) had record(s) of transplantation or rejection for one single organ. This observation is similar for other subsets.

11.2.1. Vaccine exposure

Approximately one-third of subjects received one dose of *Pandemrix* whereas 9% received two doses (Table 4 and Table 5); 36-40% of subjects received one dose of TIV across the two subsets, with approximately 20% having received two doses.

The pandemic study period extended to 31 October 2010 in order to allow sufficient control time after the end of the pandemic vaccination campaign, thus partly overlapping with the beginning of the subsequent influenza season. For subjects having received two doses of TIV in the pandemic study period, all but one subject received the “second dose” in September/October 2010 (see also Table 7).

The majority of *Pandemrix* doses were administered between end of October 2009 and end of January 2010, with a peak of vaccinations occurring during mid-November to mid-December 2009 (Figure 3), which is consistent with the publically available information on the mass vaccination campaign in the UK [Department of Health, 2010].

11.2.2. Co-administration of *Pandemrix* and TIV – primary pandemic influenza subset

During the pandemic study period, approximately 40% of subjects received both *Pandemrix* and a seasonal trivalent influenza vaccine (TIV). About 39% of subjects did not receive any influenza vaccine (Table 6). Only a small number of subjects received *Pandemrix* only (6 subjects; 3.3%) and one of these subjects received two doses of *Pandemrix*.

Co-administration of *Pandemrix* and TIV included one dose of both vaccines (34 subjects; 18.5%; Table 6), one dose of *Pandemrix* and two doses of TIV (23 subjects; 12.5%), two doses of *Pandemrix* and one dose of TIV (9 subjects; 4.9%), and two doses of both vaccines (7 subjects; 3.8%).

Table 7 describes the co-administration of *Pandemrix* and TIV, and in addition describes administration of the vaccines before and after 01-September-2010, a date that corresponds to the beginning of the influenza season subsequent to the pandemic season. Among the 73 subjects with co-administration, 42 received TIV in the season 2009-2010, 29 received TIV in both seasons 20092010 and 2010-2011, and 2 received TIV in the season 2010-2011 only. Among the 105 subjects not vaccinated with *Pandemrix*, 20 (19%) received TIV in the 2009-2010 season, 9 received seasonal vaccine in both seasons, and 4 received seasonal vaccine in the 2010-2011 season only.

Sixteen subjects received *Pandemrix* and TIV on the same day, and one additional subject received *Pandemrix* and TIV within the same week. Twenty-eight subjects received TIV within 4 weeks around the date a *Pandemrix* dose was administered (Table 8 and Table 9).

11.2.3. Co-administration of *Pandemrix* and TIV – secondary pandemic influenza subset

Approximately 40% of subjects received *Pandemrix* and TIV, and 34% of subjects did not receive any influenza vaccine (Table 10). Only a small number of subjects received *Pandemrix* only (4 subjects; 6.0%) and one of these subjects received two doses of *Pandemrix*.

Co-administration of *Pandemrix* and TIV included one dose of both vaccines (12 subjects; 17.9%; Table 10), and one dose of *Pandemrix* and two doses of TIV (8 subjects; 11.9%).

Table 11 describes the co-administration of *Pandemrix* and TIV and in addition describes the administration of the vaccines before and after 01-September-2010 which marks the beginning of the influenza season subsequent to the pandemic season. Among the 27 subjects with a co-administration, 14 received TIV in the season 2009-2010, 12 received TIV in both the season 2009-2010 and 2010-2011, and one subject received TIV in the season 2010-2011 only. Among the 36 subjects not vaccinated with *Pandemrix*, 11 (30.6%) received the TIV before 01-Sept-2010, thus in the 2009-2010 season and 1 of these 11 also received TIV in 2010-2011.

Five subjects received *Pandemrix* and TIV on the same day, and six additional subjects within the same week. Ten subjects received TIV within 4 weeks around the date a *Pandemrix* dose was administered (Table 12 and Table 13).

11.2.4. Demographic characteristics

Baseline characteristics of the study population for the primary pandemic influenza subset are given in Table 14 and Table 15:

Subjects in this subset had a mean age of 50.2 years, 45.7% were female and 5.4% were noted to have died from any cause during the pandemic study period (Table 14).

The majority of transplantations were performed prior to the 180 days before the start of the study period (i.e. before 04 April 2009) or during the pandemic study period (after 01 October 2009; 175/184 subjects), while a small proportion of the transplantations (4.9%; 9/184) occurred within the 180 days prior to the pandemic study period (between 04 April and 01 October 2009).

For 148 subjects (80.4%; Table 14), there was no record of transplantation in CPRD or HES between 04 April 2009 and 31 October 2010. Among the 36 subjects with a transplantation record, kidney was the most frequently transplanted organ (19 subjects; 10.3%) followed by liver (9 subjects; 4.9%). Information was available on concomitant

medical conditions for malignancies/cancers in 15 subjects (8.2%), and opportunistic infections in 8 subjects (4.3%). Although this patient population is at high risk of infectious diseases, events relating to infections were reported for only a small proportion.

Most of the subjects (164 subjects; 91.6%) were followed over the whole pandemic study period. The remaining subjects either died (9 subjects; 5.0%) or were no longer followed (6 subjects; 3.4%) during the study period.

Among 184 subjects, 179 subjects had at least one record of transplantation or rejection for one single organ (Table 15). Additional details can be found in Table 16 for subjects (N=5) having had more than one transplantation or rejection.

Baseline characteristics of the study population for the secondary pandemic influenza subset are described in Table 17 and Table 18. This secondary subset was further restricted to subjects with available data from the GP questionnaire (N=67 subjects). Subjects in the secondary pandemic influenza subset (subset 1b) had a mean age of 51.8 years with 44.8% being female, and 6 subjects (9.0%) were noted to have died from any cause during the pandemic period (Table 17).

The majority of transplantations were performed either during the pandemic study period (after 01 October 2009), or prior to the 180 days before the start of the study period (i.e. before 04 April 2009; 61/67 subjects), while a small proportion of the transplantations (6/67) occurred in the 180 days prior to the pandemic study period (between 04 April and 01 October 2009). For 44 subjects (65.7%), there was no record of transplantation in CPRD or HES between 04 April 2009 and 31 October 2010. Among the 23 subjects with a transplantation record, kidney was the most frequently transplanted organ (11 subjects; 16.4%) followed by liver (5 subjects; 7.5%). Information was available on concomitant medical conditions for malignancies/cancers in 2 subjects (3.0%), and respiratory infections in 3 subjects (4.5%). Chemotherapy was also recorded in this subset (8 subjects; 11.9%) because information on this type of therapy was collected in the GP questionnaire. The number of subjects who were lost to follow-up was low (1 subject; 1.5%), excluding those who died during the follow-up (6 subjects; 9.0%).

The demographic characteristics were very similar in the population of subjects with questionnaire information available, with transplantation or rejection involving only one organ (Table 18).

11.3. Outcome data

The main outcome of the study was the occurrence of SOT rejection(s) after vaccination with *Pandemrix*. The overall study population for the pandemic study period consisted of 184 subjects who had experienced a SOT rejection between 01 October 2009 and 31 October 2010. The main analyses adjusted for time since transplantation included 91 subjects, of which 71 had been exposed to *Pandemrix*. In other words, 71 cases were considered to estimate the risk of SOT rejection following vaccination with *Pandemrix*; 20 additional unexposed cases were also included to better account for time since transplantation, yielding a population of analysis of 91 subjects. The remaining subjects

(93 of 184 subjects) had no risk period associated with *Pandemrix* vaccination and no risk period associated with time since transplantation in the pandemic study period, and these subjects were excluded from the analysis (Subset 1a; Table 20).

A total of 39 subjects contributed to the analysis using data from the GP questionnaire (Subset 1b; Table 92).

11.4. Main results

11.4.1. Primary analysis for the primary objective

11.4.1.1. Number of rejections and person-time in each risk and control period associated with Pandemrix vaccination and time since transplantation

A total of 245 SOT rejections were noted in 184 subjects for the primary pandemic influenza subset (Subset 1a) indicating that multiple transplant rejections occurred in some patients as described in Table 20.

A total of 71 cases were considered to estimate the risk of SOT rejection following vaccination with *Pandemrix*; 20 additional unexposed cases were also included to better account for time since transplantation, yielding a population of analysis of 91 subjects.

Nine out of 71 rejections in exposed subjects occurred in the 0-30 day risk period after *Pandemrix* vaccination (See *Pandemrix* pooled risk periods row of Table 20).

A total of 71 out of 91 rejections occurred in the control period of >180 days after transplantation. Of the 20 cases occurring in one of the three risk periods post-transplantation (10 subjects / 8 subjects / 2 subjects in the 3 risk periods – see bottom part of Table 20), 10 rejections were noted in the 0-30-day risk period.

The number of rejections per month after transplantation was substantially reduced after the third month post-transplantation, which reflects the expected natural history post-transplantation, with the graft acquiring stability (Figure 9; see Protocol Amendment Appendix C: Feasibility Assessment).

The frequency of rejection is presented by calendar time (see Figure 10 by calendar week and Figure 11 by calendar month).

11.4.1.2. Main analysis: relative incidence of SOT rejection one month after vaccination with *Pandemrix*

The relative incidence (RI) of SOT rejection within 30 days of *Pandemrix* vaccination, compared to the control period, and adjusted for time since transplantation, is described in Table 21. No statistically significant difference was detected between the incidence rate of SOT rejection within 30 days after any *Pandemrix* dose and the incidence rate during the control period: RI = 1.05 (95% CI: 0.52, 2.14).

The RI of SOT rejection tended to decrease as time since transplantation increased: RI = 4.14 (95% CI: 0.91, 18.82) in the period 0-30 days post-transplantation; RI = 2.25 (95% CI: 0.54, 9.44) 31-90 days post-transplantation; and RI = 0.37 (95% CI: 0.06, 2.31) 91-180 days post-transplantation.

11.4.1.3. Further adjusted analyses

Additional covariates, considered as risk factors for SOT rejection (independently of *Pandemrix* vaccination) were added to the main model (see Section 11.4.1.2): see descriptive tables for TIV administration (Table 22); respiratory infections (Table 24); opportunistic infections (Table 26); acute bacterial infection (Table 28); chronic viral infections (Table 30); malignancies/cancers (Table 32); and all covariates (Table 34).

Analyses adjusted for time since transplantation and some of the covariates were not conducted because there were less than 5 subjects exposed per covariate: respiratory infection (N=2); acute bacterial infection and chronic viral infections (N=0).

With the model adjusted for time since transplantation and TIV administration, the RI of SOT rejection within 30 days of *Pandemrix* vaccination was 1.17 (95% CI: 0.57, 2.39) (Table 23). The model adjusted for time since transplantation and opportunistic infections yielded a RI of 1.06 (95% CI: 0.52, 2.15) (Table 27). The model adjusted for time since transplantation and malignancies/cancers yielded a RI of 1.13 (95% CI: 0.56, 2.30) (Table 33).

When all these covariates were included in a single multivariable model, the RI within 30 days of *Pandemrix* vaccination was 1.29 (95% CI: 0.63, 2.63) (Table 35). The model adjusted for time since transplantation and TIV administration yielded a RI of 0.38 (0.15, 0.98). Similar trends in RI of SOT rejection post-transplantation were observed in all analyses.

11.4.1.4. Sensitivity analyses for the primary objective

Since rejection might affect the likelihood of subsequent vaccination, the case-series analysis for perturbed post-event exposure was used (see Section 10.9.2.3). However, the standard SCCS method was used in sensitivity analyses to assess the consistency in risk estimates between the two methods.

In this analysis (based on Subset 1a), 72 subjects were exposed to *Pandemrix* and a total of 11 subjects had a rejection in the day 0-30 risk period after *Pandemrix* vaccination (Table 36). Note two extra subjects with rejections in the day 0-30 risk period compared to the main primary analysis (Table 20), which can be explained by the standard method not requiring censoring at a subsequent rejection, thus potentially allowing for multiple events to be included in the analysis.

The observed RI estimate for *Pandemrix* vaccination in the main analysis (RI = 1.05; Table 21) was little affected when using the standard SCCS method (not accounting for perturbed post-event exposure): RI = 1.11 (95% CI: 0.59, 2.09; Table 37).

11.4.2. Secondary analyses for the primary objective

11.4.2.1. Number of rejections and person-time in each risk and control period associated with Pandemrix vaccination and time since transplantation

Subset 1b encompasses subjects for whom combined information from the returned GP questionnaires, CPRD and HES is available - see Section 10.5.3 of the Methods, and Table 1 and Section 11.1 of the Results for details of the response rate for the GP questionnaires.

A total of 95 SOT rejections were noted in 67 subjects for the secondary pandemic influenza subset (Subset 1b) as described in Table 92.

A total of 39 cases were considered to estimate the risk of SOT rejection following vaccination with *Pandemrix* or following transplantation (Table 92), of which 26 were exposed to *Pandemrix.* A total of 3 subjects had a rejection in the day 0-30 risk period after *Pandemrix* vaccination. Most of these 39 SOT rejections occurred in the reference period of >180 days after transplantation (26 rejections). Of the 13 cases occurring in one of the three risk periods post-transplantation, 6 rejections were noted in the 0-30-day risk period.

As in Subset 1a, the number of rejections per month after transplantation was substantially reduced after the third month post-transplantation (Figure 13 and Figure 14). The frequency of rejection is presented by calendar time (Figure 15 and Figure 16)

11.4.2.2. Main analysis: relative incidence of SOT rejection one month after vaccination with *Pandemrix*

The RI of SOT rejection within 30 days of *Pandemrix* vaccination, compared to the control period, and adjusted for time since transplantation, is described in Table 93. No difference was detected between the incidence rate of SOT rejection within 30 days after any *Pandemrix* dose and the incidence rate during the control period: RI = 0.70 (95% CI: 0.23, 2.11) (Table 93), similar to the RI observed with Subset 1a (Table 21).

As in Subset 1a, the incidence of SOT rejection tended to decrease as time since transplantation increased, although the magnitude of the decline was slightly smaller: RI = 2.09 (95% CI: 0.36, 12.04; Table 93) in the period 0-30 days post-transplantation; RI = 1.61 (95% CI: 0.38, 6.72) 31-90 days post-transplantation; and RI = 0.42 (95% CI: 0.05, 3.45) 91-180 days post-transplantation.

11.4.2.3. Further adjusted analyses

Besides the covariates described in the adjusted analyses for Subset 1a, information on chemotherapy not available in the CPRD or HES was collected from the GP questionnaires - see tables for TIV administration (Table 94 and Table 95); respiratory infections (Table 96 and Table 97); opportunistic infections (Table 98 and Table 99); acute bacterial infection (Table 100 and Table 101); chronic viral infections (Table 102 and Table 103); malignancies/cancers (Table 104 and Table 105); chemotherapy (Table 106 and Table 107) and all covariates (Table 108 and Table 109).

The GP questionnaire also intended to collect qualitative data on subjects' compliance to immunosuppressive treatment; however, this information was poorly documented by the GPs, and therefore not usable.

With the model adjusted for time since transplantation and seasonal influenza vaccination, the RI of SOT rejection within 30 days of *Pandemrix* vaccination was 0.75 (95% CI: 0.26, 2.22; Table 95); for chemotherapy, the RI was 0.72 (95% CI: 0.24, 2.16; Table 107). When these covariates were all included in the model, the RI was 0.77 (95% CI: 0.26, 2.27; Table 109).

The 95% CI for the chemotherapy RI was the only 95% CI which did not include 1.0: RI = 0.07 (95% CI: 0.01, 0.91; Table 107).

Analyses with covariates other than chemotherapy and TIV administration were not conducted because there were less than 5 subjects exposed per covariate.

11.4.3. Exploratory analyses for the primary objective

A previous SOT rejection might influence the risk of a subsequent rejection. Therefore it can be assumed that the risk of rejection might differ between subjects having already experienced a rejection and those who haven't. The effect of a previous rejection could also be time-dependent – see Section 10.9.2.3.1.

It was planned to test the modifying effect of a previous rejection by introducing an interaction term between the fixed effect of a previous rejection and the time-varying effect of vaccination in the model (10.9.2.3.1).

Subset 1a

Due to the small number of subjects having experienced a previous rejection (N=9; Table 41 and Table 42), the estimates associated with the model that included the interaction term could not be calculated (Table 38). However, separate analyses only including subjects without previous rejections (N=82) are presented in Table 39 and Table 40; these sub-analyses are important to more finely estimate the effect of exposure to *Pandemrix*, limiting the potential confounding effect of previous rejection(s). No difference was detected between the incidence rate of SOT rejection within 30 days after any *Pandemrix* dose and the incidence rate during the control period: RI = 1.02 (95% CI: 0.48, 2.13).

Subset 1b

Similarly to Subset 1a, only analyses including subjects without previous rejections could be conducted (N= 33 including 20 exposed cases; Table 113). No difference was detected between the incidence rate of SOT rejection within 30 days after any *Pandemrix* dose and the incidence rate during the control period: RI = 0.43 (95% CI: 0.15, 1.25) (Table 114).

11.4.4. Exploratory analyses for the primary objective by organ

Subset 1a

There were insufficient subjects identified to calculate the RI values for all individual organs but kidney: heart (N=8 including 4 exposed cases; Table 43); liver (N=19 including 6 exposed cases; Table 67); lung (N=5 including 3 exposed cases; Table 90); and pancreas (N=1 exposed case; Table 91). Overall results of the analyses including all organs were thus mainly driven by kidney (N=97 including N=53 exposed cases; Table 44).

In the main analysis, the RI of SOT rejection within 30 days of *Pandemrix* vaccination, compared to the control period, and adjusted for time since transplantation, was 0.85 (95% CI: 0.38, 1.90) for kidney (Table 45). The RI was 1.00 (95% CI: 0.44, 2.25) in the model adjusted for all covariates (only information on TIV administration and malignancies/cancers was available) (Table 59). Restricting the analysis to subjects without previous rejections (N=58 including 46 exposed cases; Table 63), the RI was 0.71 (95%CI: 0.30, 1.64) (Table 64).

Subset 1b

Similarly to Subset 1a, only analyses for kidney could be conducted (N=34 including N=18 exposed cases; Table 118).

In the main analysis, the RI of SOT rejection within 30 days of *Pandemrix* vaccination, compared to the control period, and adjusted for time since transplantation, was 0.58 (95% CI: 0.18, 1.89) for kidney (Table 119). The RI was 0.56 (95% CI: 0.21, 1.50) in the model adjusted for all covariates (only information on TIV administration was available) (Table 135). Restricting the analysis to subjects without previous rejections (N=22 including 14 exposed cases; Table 139), the RI was 0.10 (95%CI: 0.08, 0.12) (Table 140).

11.4.5. Secondary objective

Subset 1a

Overall, results of analyses using a two-month risk period did not substantially differ from those with a one-month risk period.

A total of 72 exposed cases were considered to estimate the risk of SOT rejection following vaccination with *Pandemrix* (one additional case compared to the primary objective) (Table 147).

The relative incidence (RI) of SOT rejection within 60 days of *Pandemrix* vaccination, compared to the control period, and adjusted for time since transplantation, is described in Table 148. No difference was detected between the incidence rate of SOT rejection within 60 days after any *Pandemrix* dose and the incidence rate during the control period: RI = 0.80 (95% CI: 0.42, 1.50).

With the model adjusted for all covariates (information available for TIV administration, opportunistic infections, malignancies/cancers), the RI was 0.91 (95% CI: 0.49, 1.70) (Table 162).

Similar trends in RI of SOT rejection post-transplantation (RI of SOT rejection tending to decrease as time since transplantation increased) were observed in all analyses, compared to the analyses for the primary objective.

When applying the standard SCCS method, the RI was 0.96 (95% CI: 0.58, 1.61) (Table 164).

Restricting the analysis to subjects without previous rejections, the RI was 0.74 (95% CI: 0.37, 1.48) (Table 167).

In the analyses by organ, the RI for kidney was 0.68 (95% CI: 0.33, 1.40) (Table 172).

Subset 1b

Overall, results of analyses using a two-month risk period did not substantially differ from those with a one-month risk period.

A total of 26 exposed cases were considered to estimate the risk of SOT rejection following vaccination with *Pandemrix* (Table 219).

The relative incidence (RI) of SOT rejection within 60 days of *Pandemrix* vaccination, compared to the control period, and adjusted for time since transplantation, is described in Table 220. No difference was detected between the incidence rate of SOT rejection within 60 days after any *Pandemrix* dose and the incidence rate during the control period: RI = 0.64 (95% CI: 0.26, 1.58).

With the model adjusted for all covariates (information available for TIV administration, chemotherapy), the RI was 0.67 (95% CI: 0.28, 1.63) (Table 236).

Similar trends in RI of SOT rejection post-transplantation (RI of SOT rejection tending to decrease as time since transplantation increased) were observed in all analyses, compared to the analyses for the primary objective.

When applying the standard SCCS method, the RI was 0.69 (95% CI: 0.26, 1.81) (Table 238).

Restricting the analysis to subjects without previous rejections, the RI was 0.37 (95% CI: 0.12, 1.18) (Table 241).

In the analyses by organ, the RI for kidney was 0.70 (95% CI: 0.28, 1.76) (Table 246).

11.5. Other analyses

Not applicable.

11.6. Adverse events/adverse reactions

Not applicable.

12. DISCUSSION

The present study was designed to address a safety signal that emerged following spontaneous case reports of SOT rejection shortly after the 2009 H1N1 influenza pandemic and the ensuing mass vaccination campaigns in Europe and Canada; published reports described cases temporally associated with vaccination. The study was conducted in the UK, where *Pandemrix* was the main vaccine administered during the pandemic.

To our knowledge, this is the first pharmaco-epidemiological study designed to assess the risk of rejection following vaccination with a H1N1 pandemic influenza vaccine.

12.1. Key results

The overall study population for the pandemic study period consisted of 184 subjects in CPRD-HES who had experienced a SOT rejection between 01 October 2009 and 31 October 2010. The main analyses included 91 subjects, of which 71 had been exposed to *Pandemrix*. In the main analyses, which were adjusted for time since transplantation, results indicate a relative incidence of SOT rejection within one month after vaccination with *Pandemrix* of 1.05 (95%CI: 0.52, 2.14), and a RI of 0.80 (95% CI: 0.42, 1.50) within two months after vaccination.

These estimates remained stable across several sensitivity and exploratory analyses. In the analysis subsets that incorporated subjects for which GP questionnaire information was available and valid, the range of risk estimates was also similar.

Time since transplantation appears as a critical factor impacting the risk of transplant rejection, with a substantially higher risk of rejection in the first 3-month period

post-transplantation (see study protocol - Appendix C – Feasibility assessment). This was further suggested in the analyses examining the RI of SOT rejection associated with time since transplantation, which consistently tended to decrease with increasing time since transplantation. Consequently, time since transplantation was hypothesized to be a confounding factor and was included in all statistical models. However, because 63 of 71 exposed subjects received their transplantation >180 days prior to the beginning of the pandemic study period (data not tabulated) - implying that most subjects contributed only to the control period to exposure of “time since transplantation” - the effect of the other categories of time since transplantation (0-30; 31-90; 91-180 days) could not be estimated. Therefore, time since transplantation did not appear as a confounding factor as measured in the present study.

Another design assumption was that previous rejection(s) might modify the risk of a subsequent rejection. Therefore, several analyses were performed attempting to separately estimate the risk of rejection in subjects who did or did not experience rejection(s) in the 6 months before the beginning of the study period. However, since the large majority of subjects had no previous rejection in the 6-month period prior to study period, the effect of this potential confounder were likely to be negligible; the risk estimates for this strata were consistent with the overall risk estimates.

Some studies indicate that risk factors for rejection, and the magnitude of the risk, might vary by organ type [Klein, 2011]; however, given the small numbers in analyses when stratified by organ type, the risk of rejection by organ could only be assessed individually for the kidney, with a RI of rejection of 0.85 (95% CI: 0.38-1.90) one month after vaccination. Nonetheless, these organ specific estimates for the kidney are informative for public health decision making given that the kidney is the most commonly transplanted organ in the UK (European Society for Organ Transplantation, 2013).

As the effect of *Pandemrix* might be confounded by seasonal influenza vaccination, several analyses were adjusted for this variable. Results thereof showed no difference from the main risk estimates. Because a large proportion of subjects in these analyses did not receive the pandemic and the seasonal vaccine concomitantly (i.e., on the same day), this allowed an independent estimation of the risk associated with *Pandemrix* and the adjustment for the potential confounding effect of seasonal vaccination.

12.2. Strengths and Limitations

12.2.1. Strengths

The study was set up in both the CPRD GOLD and its linked component of the HES database. HES contains in- and outpatient information for all NHS hospitals in the UK, which maximised the likelihood of capturing cases with an outcome clinically managed in specialty/hospital settings, in this case SOT rejection. In addition, diagnosis data recorded in HES is based on a standardised coding system (i.e. ICD-10 clinical coding and OPCS4 procedural coding), thus ensuring consistent information across the study population.

The high proportion of subjects having a HES link (93%) confirmed the adequacy of using HES as the gold standard for the primary analysis, compared to the study design in the original protocol (see Section 9) where the gold standard for the analyses was the GP questionnaire.

The CPRD GOLD has been extensively used in pharmaco-epidemiological research, with data internally and externally validated for various outcomes [Herrett, 2010]. It is a large dataset with good representativeness of GPs throughout the UK; age-gender composition of registered individuals is very similar to that of the UK general population. In addition, the primary health care system in the UK covers a comprehensive population, and the patient population captured in the CPRD GOLD is broadly representative of the demographic structure of the UK population.

During the 2009 H1N1 influenza pandemic vaccination campaign, immunisation was administered in the majority of cases by GPs; therefore, vaccine uptake in the CPRD GOLD is likely to accurately represent uptake in the UK, and individual vaccination data is considered to be accurately and comprehensively captured.

Pandemic vaccination codes described as both GSK manufactured and with an unbranded/ unknown manufacturer were considered, as recommended by EMA. Both *Pandemrix* and *Celvapan* (Baxter) were used in the UK; however, according to UK data [Department of Health, 2010] and feasibility data from the CPRD GOLD (see protocol: Appendix C), only 0.1% of individuals received *Celvapan*. Thus, the risk of misclassification of exposure was considered marginal and immunisation data in this study primarily reflects the uptake of *Pandemrix*.

With 30 expected exposed cases, the study was designed to have 80% statistical power to detect a RI of 3.0 or higher (Section 10.7). Considering that 71 exposed cases were included in the main analyses, it can be assumed that the study was powered to reliably address the research question.

SOT rejection is a complex outcome, affected by several potential risk factors. The SCCS design implicitly controls for fixed confounders, i.e., that do not vary with time over the observation period (healthcare seeking behaviour, access to healthcare, individual frailty and severity of underlying conditions), also precluding indication bias.

12.2.2. Limitations

SOT rejections were identified using a standardised coding system (i.e. ICD-10 clinical coding and OPCS4 procedural coding). Per original study protocol, SOT rejections were to be confirmed by the GP via a standardized questionnaire. However, this confirmation appeared to be unfeasible because of the high proportion of returned questionnaires that were incomplete. Based on the information received from the GPs, transplant rejection events appeared to be under-reported and under-documented, with GPs reporting less than 40% of the number of transplant rejections initially identified in the CPRD-HES. GP responses suggested that the questionnaires do not comprehensively and systematically capture SOT rejection, possibly because transplant rejection is handled in specialty/hospital settings.

SOT rejection is a complex and heterogeneous clinical entity; the likelihood of occurrence is affected by multiple factors. Those include viral (including H1N1 influenza virus and seasonal infections) and bacterial infections, co-morbidities, underlying medical conditions, medical history of the transplant recipient and compliance to immunosuppressive treatment.

There was an attempt in the study to collect such information; however, the number of records for infections and malignancies/cancers appeared to be limited in the CPRD, and the GP questionnaire, which was aimed at collecting similar information (assumed to be better documented at the GP level) yielded very limited information. The GP questionnaire also intended to collect qualitative data on type of transplant rejection, immunological mechanism and subjects' compliance to immunosuppressive treatment, a known risk factor for rejection; however, this information was poorly documented by the GPs and not usable. Confounding by those factors could not be evaluated. However, it is unlikely to have introduced systematic error into the present study.

The risk of rejection might be modified depending on the number of pandemic vaccine doses received. However, in the present study the proportion of subjects receiving two doses is low and did not allow for a reliable separate assessment of the effect of the second dose while adjusting for time since transplantation.

To our knowledge, the risk period for transplant rejection following vaccination is unknown. With the SCCS design, a short risk period could result in an underestimated RI because of residual risk effect during the control period. On the other hand, a longer risk period could dilute a possible risk and also results in an underestimation of the RI. In our design, the one-month risk period is based on the latency observed in spontaneous cases reported to GSK; it also corresponds to the most common risk period for rejection following other exposures such as infection. The two-month risk period was also considered to ensure that the estimates were not impacted by a longer risk period.

12.2.3. Interpretation

Data from this study, which showed a consistent range of risk estimates all in the vicinity of 1.0 with an upper 95% confidence limit around 2.0, suggest no evidence of an increased risk of SOT rejection one and two months following vaccination with *Pandemrix* in the UK.

12.3. Generalisability

Given the representativeness of the CPRD and HES, results from this study could be extrapolated to the overall population of SOT recipients in the UK. Although standards of care of transplanted patients might vary within the UK, documentation/coding guidelines in HES are standardised, hence limiting the variability in patient level information.

However, although the results appeared to be robust and showed a high degree of consistency across the different analyses, the SCCS design does now allow to directly generalise the conclusions beyond the population included in the analyses.

While a composite of organs were considered in the present study, a substantial proportion of subjects who contributed to calculate the risk estimates received kidney transplantation, resulting in risk estimates mainly accounting for this organ and limiting the possibility to generalise the results to other types of SOT.

13. OTHER INFORMATION

The study results are to be reported both internally within GSK and externally to EMA, and a manuscript will be submitted to a peer-reviewed journal for publication. A result summary will be posted to the GSK Clinical Study Register and the EU PAS register.

14. CONCLUSION

Data from this study, which showed a consistent range of risk estimates all in the vicinity of 1.0, suggest no evidence of an increased risk of SOT rejection one and two months following vaccination with *Pandemrix* in the UK.

The results do not suggest a change in the benefit-risk profile of *Pandemrix*.

In conclusion, this study provides important safety data to inform the benefit-risk of an ASO3-adjuvanted pandemic influenza vaccine in transplanted patients in the event of a future pandemic.

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16. APPENDICES

Table 1 Selection of the study population for the pandemic influenza study period (Total cohort)

Title	Total	Percent
Subjects with SOT rejection identifier(s) in the CPRD GOLD or HES during the study period (2006-2010)	587	-
Subjects with HES link	545	92.84
Subjects with a follow-up for season 2009-2010 and with at least one SOT rejection in HES between 01-Oct-2009 and 31-Oct-2010 (subset 1a)	184	31.35
Subjects with GP questionnaire returned and usable	161	27.43
Subjects with a follow-up for season 2009-2010 and with at least one SOT rejection in CPRD GOLD, HES or GP questionnaire between 01-Oct-2009 and 31-Oct-2010 (subset 1b)	67	11.41

Note: a subject has a follow-up for the pandemic season if his follow-up in the CPRD GOLD and in HES includes 01 October 2009 and the preceding 180 days period.

Table 2 Distribution of subjects and person-time into each influenza study period for each subset (Total cohort)

Subset	Influenza season	N	%	Person-years
Primary pandemic influenza subset	2009/2010	184	-	192.82
Secondary pandemic influenza subset	2009/2010	67	-	70.38
Primary seasonal influenza subset	2006 - 2009	375	-	359.90
	2006/2007	132	35.20	125.88
	2007/2008	136	36.27	132.01
	2008/2009	168	44.80	159.47
Secondary seasonal influenza subset	2006 - 2009	140	-	133.92
	2006/2007	48	34.29	45.21
	2007/2008	55	39.29	53.64
	2008/2009	67	47.86	63.32

N: Number of subjects considered in the influenza season
%: Percentage of subjects considered in the influenza season in the corresponding subset

Table 3 Distribution of subjects and person-time into each influenza study period for each subset (Total cohort, subjects with transplantation or rejection for only one organ)

Subset	Influenza season	N	%	Person-years
Primary pandemic influenza subset	2009/2010	179	-	187.91
Secondary pandemic influenza subset	2009/2010	63	-	66.55
Primary seasonal influenza subset	2006 - 2009	363	-	347.88
	2006/2007	130	35.81	123.88
	2007/2008	128	35.26	123.99
	2008/2009	163	44.90	154.47
Secondary seasonal influenza subset	2006 - 2009	133	-	126.91
	2006/2007	45	33.83	42.21
	2007/2008	52	39.10	50.63
	2008/2009	63	47.37	59.32

N: Number of subjects considered in the influenza season
%: Percentage of subjects considered in the influenza season in the corresponding subset

Table 4 Description of vaccine exposure in the pandemic influenza study period (Total cohort)

Subset	Influenza vaccine	Vaccination	N	n	%
Primary pandemic influenza subset	Pandemrix TM	Not vaccinated	184	105	57.07
		1 dose	184	62	33.70
		2 doses	184	17	9.24
	Seasonal	Not vaccinated	184	78	42.39
		1 dose	184	67	36.41
		2 doses	184	39	21.20
Secondary pandemic influenza subset	Pandemrix TM	Not vaccinated	67	36	53.73
		1 dose	67	23	34.33
		2 doses	67	8	11.94
	Seasonal	Not vaccinated	67	27	40.30
		1 dose	67	27	40.30
		2 doses	67	13	19.40

N: Number of subjects in the subset
n/%: Number/Percentage of subjects in each category

Table 5 Description of vaccine exposure in the pandemic influenza study period (Total cohort, subjects with transplantation or rejection for only one organ)

Subset	Influenza vaccine	Vaccination	N	n	%
Primary pandemic influenza subset	Pandemrix TM	Not vaccinated	179	103	57.54
		1 dose	179	59	32.96
		2 doses	179	17	9.50
	Seasonal	Not vaccinated	179	77	43.02
		1 dose	179	64	35.75
		2 doses	179	38	21.23
Secondary pandemic influenza subset	Pandemrix TM	Not vaccinated	63	34	53.97
		1 dose	63	21	33.33
		2 doses	63	8	12.70
	Seasonal	Not vaccinated	63	26	41.27
		1 dose	63	25	39.68
		2 doses	63	12	19.05

N: Number of subjects in the subset
n/%: Number/Percentage of subjects in each category

Figure 3 Frequency of Pandemrix vaccinations per calendar week (Subset 1a)

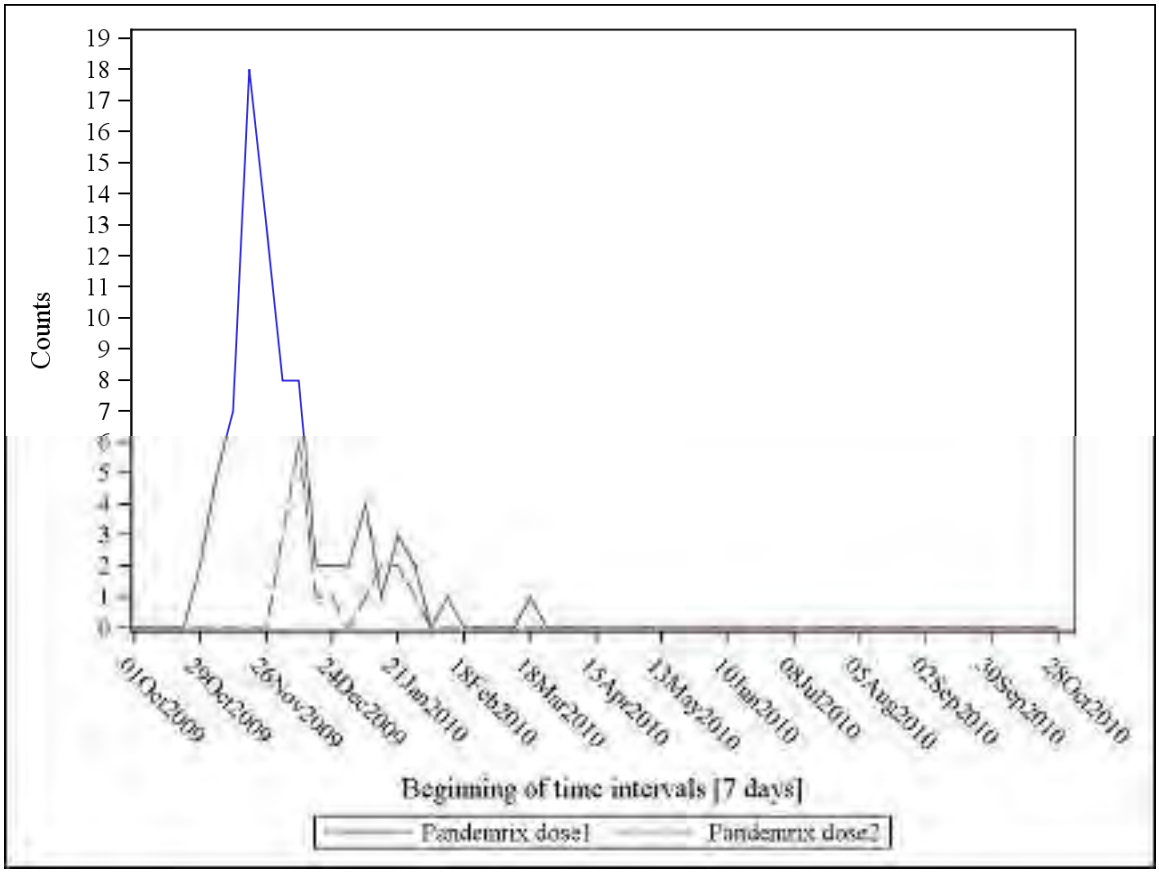

Figure 4 Frequency of Pandemrix vaccinations per calendar month (Subset 1a)

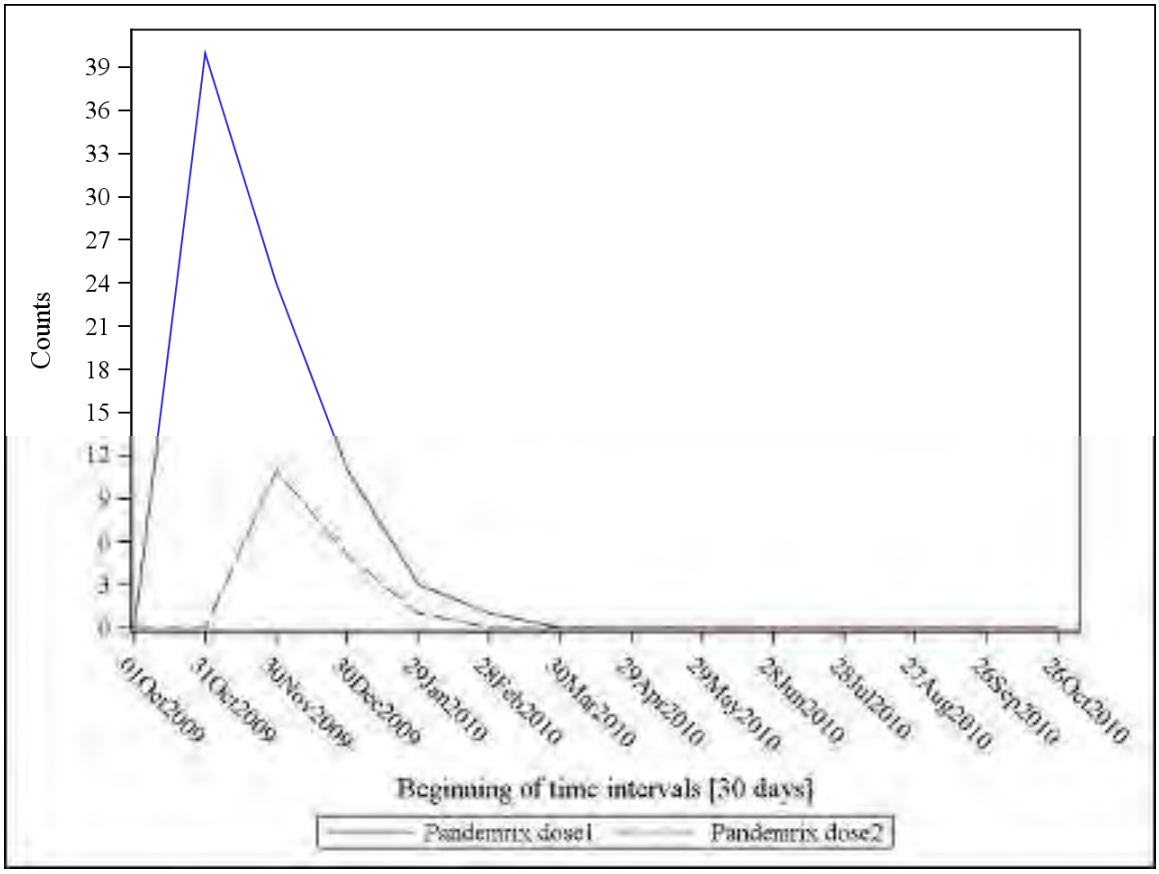

Table 6 Co-administrations of Pandemrix and seasonal influenza vaccine during the pandemic influenza study period (Subset 1a)

		N=184	
Characteristics	Categories	n	%
Co-administrations	No vaccination	72	39.1
	Pandemrix only	6	3.3
	Seasonal only	33	17.9
	Pandemrix and seasonal	73	39.7
Details of co-administrations	No vaccination	72	39.1
	Pandemrix 1 dose	5	2.7
	Pandemrix 2 doses	1	0.5
	Seasonal 1 dose	24	13.0
	Seasonal 2 doses	9	4.9
	Pandemrix 1 dose - Seasonal 1 dose	34	18.5
	Pandemrix 1 dose - Seasonal 2 doses	23	12.5
	Pandemrix 2 doses - Seasonal 1 dose	9	4.9
	Pandemrix 2 doses - Seasonal 2 doses	7	3.8

N: Number of subjects in the subset
n/%: Number/Percentage of subjects in each category

Table 7 Details of vaccination with Pandemrix and seasonal influenza vaccine between 01-Oct-2009 and 31-Oct-2010 (Subset 1a)

				N=184	
Number of doses of Pandemrix before 01-Sep-10	Number of doses of Pandemrix after 01-Sep-10	Number of doses of seasonal vaccine before 01-Sep-10	Number of doses of seasonal vaccine after 01-Sep-10	n	%
0	0	0	0	72	39.1
			1	4	2.2
		1	0	20	10.9
			1	9	4.9
1	0	0	0	5	2.7
			1	1	0.5
		1	0	33	17.9
			1	22	12.0
		2	0	1	0.5
2	0	0	0	1	0.5
			1	1	0.5
		1	0	8	4.3
			1	7	3.8

N: Number of subjects in the subset
n/%: Number/Percentage of subjects in each category

Table 8 Time between first doses of Pandemrix and seasonal influenza vaccine in subjects with co-administration (Subset 1a)

		N=73	
Characteristics	Categories	n	%
Pandemrix and seasonal on the same day	Yes	16	21.9
	No	57	78.1
Time between Pandemrix and seasonal [weeks]	-21	1	1.4
	-14	2	2.7
	-13	2	2.7
	-12	1	1.4
	-11	1	1.4
	-10	1	1.4
	-9	2	2.7
	-8	5	6.8
	-7	6	8.2
	-6	6	8.2
	-5	11	15.1
	-4	5	6.8
	-3	6	8.2
	-2	1	1.4
	-1	3	4.1
	0	17	23.3
	2	1	1.4
	37	1	1.4
	44	1	1.4

N: Number of subjects with Pandemrix and seasonal influenza vaccine
n/%: Number/Percentage of subjects in each category
The weekly interval between Pandemrix and seasonal is computed as (seasonal date - Pandemrix date)/7

Table 9 Minimum of time between Pandemrix and seasonal influenza vaccine in subjects with co-administration (Subset 1a)

		N=73	
Characteristics	Categories	n	%
Pandemrix and seasonal on the same day	Yes	16	21.9
	No	57	78.1
Minimum of time between Pandemrix and seasonal [weeks]	-21	1	1.4
	-14	2	2.7
	-13	2	2.7
	-12	1	1.4
	-11	1	1.4
	-10	1	1.4
	-9	2	2.7
	-8	5	6.8
	-7	6	8.2
	-6	6	8.2
	-5	11	15.1
	-4	5	6.8
	-3	6	8.2
	-2	1	1.4
	-1	3	4.1
	0	17	23.3
	2	1	1.4
	37	1	1.4
	41	1	1.4

N: Number of subjects with Pandemrix and seasonal influenza vaccine
n/%: Number/Percentage of subjects in each category
The weekly interval between Pandemrix and seasonal is computed as (seasonal date - Pandemrix date)/7

Table 10 Co-administrations of Pandemrix and seasonal influenza vaccine during the pandemic influenza study period (Subset 1b)

		N=67	
Characteristics	Categories	n	%
Co-administrations	No vaccination	23	34.3
	Pandemrix only	4	6.0
	Seasonal only	13	19.4
	Pandemrix and seasonal	27	40.3
Details of co-administrations	No vaccination	23	34.3
	Pandemrix 1 dose	3	4.5
	Pandemrix 2 doses	1	1.5
	Seasonal 1 dose	12	17.9
	Seasonal 2 doses	1	1.5
	Pandemrix 1 dose - Seasonal 1 dose	12	17.9
	Pandemrix 1 dose - Seasonal 2 doses	8	11.9
	Pandemrix 2 doses - Seasonal 1 dose	3	4.5
	Pandemrix 2 doses - Seasonal 2 doses	4	6.0

N: Number of subjects in the subset
n/%: Number/Percentage of subjects in each category

Table 11 Details of vaccination with Pandemrix and seasonal influenza vaccine between 01-Oct-2009 and 31-Oct-2010 (Subset 1b)

				N=67	
Number of doses of Pandemrix before 01-Sep-10	Number of doses of Pandemrix after 01-Sep-10	Number of doses of seasonal vaccine before 01-Sep-10	Number of doses of seasonal vaccine after 01-Sep-10	n	%
0	0	0	0	23	34.3
			1	2	3.0
		1	0	10	14.9
			1	1	1.5
1	0	0	0	3	4.5
		1	0	12	17.9
			1	8	11.9
2	0	0	0	1	1.5
			1	1	1.5
		1	0	2	3.0
			1	4	6.0

N: Number of subjects in the subset
n/%: Number/Percentage of subjects in each category

Table 12 Time between first doses of Pandemrix and seasonal influenza vaccine in subjects with co-administration (Subset 1b)

		N=27	
Characteristics	Categories	n	%
Pandemrix and seasonal on the same day	Yes	5	18.5
	No	22	81.5
Time between Pandemrix and seasonal [weeks]	-21	1	3.7
	-14	1	3.7
	-13	1	3.7
	-11	1	3.7
	-10	1	3.7
	-8	1	3.7
	-7	4	14.8
	-6	1	3.7
	-5	4	14.8
	-4	1	3.7
	-3	3	11.1
	-1	1	3.7
	0	6	22.2
	44	1	3.7

N: Number of subjects with Pandemrix and seasonal influenza vaccine
n/%: Number/Percentage of subjects in each category
The weekly interval between Pandemrix and seasonal is computed as (seasonal date - Pandemrix date)/7

Table 13 Minimum of time between Pandemrix and seasonal influenza vaccine in subjects with co-administration (Subset 1b)

		N=27	
Characteristics	Categories	n	%
Pandemrix and seasonal on the same day	Yes	5	18.5
	No	22	81.5
Minimum of time between Pandemrix and seasonal [weeks]	-21	1	3.7
	-14	1	3.7
	-13	1	3.7
	-11	1	3.7
	-10	1	3.7
	-8	1	3.7
	-7	4	14.8
	-6	1	3.7
	-5	4	14.8
	-4	1	3.7
	-3	3	11.1
	-1	1	3.7
	0	6	22.2
	41	1	3.7

N: Number of subjects with Pandemrix and seasonal influenza vaccine co-administered
n/%: Number/Percentage of subjects in each category
The weekly interval between Pandemrix and seasonal is computed as (seasonal date - Pandemrix date)/7

Table 14 Demographic and baseline characteristics (Subset 1a)

		nvac N = 105		vac N = 79		Total N = 184	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Age at 01-Oct-2009 [years]	N	105	-	79	-	184	-
	Mean	49.3	-	51.3	-	50.2	-
	SD	21.58	-	14.54	-	18.86	-
	Median	52.0	-	53.0	-	52.0	-
	Minimum	1	-	9	-	1	-
	Maximum	89	-	91	-	91	-
Age group at 01-Oct-2009 [years]	[0-17]	9	8.6	3	3.8	12	6.5
	[18-44]	33	31.4	20	25.3	53	28.8
	[45-60]	31	29.5	32	40.5	63	34.2
	61+	32	30.5	24	30.4	56	30.4
Gender	Female	51	48.6	33	41.8	84	45.7
	Male	54	51.4	46	58.2	100	54.3
Died between 01-Oct-2009 and 31-Oct-2010	No	99	94.3	75	94.9	174	94.6
	Yes	6	5.7	4	5.1	10	5.4
Time since transplantation at 01-Oct-2009 [days]	Before transplantation or more than 180 days after transplantation	103	98.1	72	91.1	175	95.1
	0-30	2	1.9	2	2.5	4	2.2
	31-90	0	0.0	1	1.3	1	0.5
	91-180	0	0.0	4	5.1	4	2.2
Organ transplanted before or during the season**	Heart	0	0.0	1	1.3	1	0.5
	Kidney	10	9.5	9	11.4	19	10.3
	Kidney+Liver	2	1.9	0	0.0	2	1.1
	Kidney+Pancreas	0	0.0	2	2.5	2	1.1
	Liver	6	5.7	3	3.8	9	4.9
	Lung	0	0.0	2	2.5	2	1.1
	Pancreas	0	0.0	1	1.3	1	0.5
	No transplantation recorded	87	82.9	61	77.2	148	80.4
Number of rejections between 04-Apr-2009 and 01-Oct-2009	None	91	86.7	70	88.6	161	87.5
	At least one	14	13.3	9	11.4	23	12.5
Number of transplantation events between 01-Oct-2009 and 31-Oct-2010	0	89	84.8	67	84.8	156	84.8
	1	13	12.4	11	13.9	24	13.0
	2	2	1.9	1	1.3	3	1.6
	4	1	1.0	0	0.0	1	0.5
Respiratory infection[s] between 01-Sep-2009 and 31-Oct-2010	No	105	100	77	97.5	182	98.9
	Yes	0	0.0	2	2.5	2	1.1
Acute bacterial infection[s] between 01-Sep-2009 and 31-Oct-2010	No	105	100	79	100	184	100
	Yes	0	0.0	0	0.0	0	0.0
Opportunistic infection[s] between 01-Sep-2009 and 31-Oct-2010	No	103	98.1	73	92.4	176	95.7
	Yes	2	1.9	6	7.6	8	4.3
Chronic viral infection[s] between 01-Oct-2008 and 31-Oct-2010	No	105	100	79	100	184	100
	Yes	0	0.0	0	0.0	0	0.0
Malignancy/cancer[s] between 01-Oct-2008 and 31-Oct-2010	No	99	94.3	70	88.6	169	91.8
	Yes	6	5.7	9	11.4	15	8.2
Reasons for end of follow-up	End of pandemic study period [31-Oct-2010]	94	89.5	74	93.7	168	91.3
	Death	6	5.7	4	5.1	10	5.4
	End of CRPD GOLD follow-up	5	4.8	1	1.3	6	3.3

nvac = no Pandemrix
vac = Pandemrix

**Each subject is classified in one category. All combinations are possible. Only transplantations between 04-Apr-2009 and 31-Oct-2010 are taken into account
n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD = Standard deviation

Table 15 Demographic and baseline characteristics (Subset 1a, subjects with transplantation or rejection for only one organ)

		nvac N = 103		vac N = 76		Total N = 179	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Age at 01-Oct-2009 [years]	N	103	-	76	-	179	-
	Mean	49.6	-	51.9	-	50.6	-
	SD	21.56	-	14.52	-	18.88	-
	Median	52.0	-	53.5	-	52.0	-
	Minimum	1	-	9	-	1	-
	Maximum	89	-	91	-	91	-
Age group at 01-Oct-2009 [years]	[0-17]	9	8.7	3	3.9	12	6.7
	[18-44]	32	31.1	17	22.4	49	27.4
	[45-60]	30	29.1	32	42.1	62	34.6
	61+	32	31.1	24	31.6	56	31.3
Gender	Female	50	48.5	31	40.8	81	45.3
	Male	53	51.5	45	59.2	98	54.7
Died between 01-Oct-2009 and 31-Oct-2010	No	97	94.2	73	96.1	170	95.0
	Yes	6	5.8	3	3.9	9	5.0
Time since transplantation at 01-Oct-2009 [days]	Before transplantation or more than 180 days after transplantation	101	98.1	71	93.4	172	96.1
	0-30	2	1.9	2	2.6	4	2.2
	31-90	0	0.0	1	1.3	1	0.6
	91-180	0	0.0	2	2.6	2	1.1
Organ transplanted before or during the season**	Heart	0	0.0	1	1.3	1	0.6
	Kidney	10	9.7	9	11.8	19	10.6
	Liver	6	5.8	3	3.9	9	5.0
	Lung	0	0.0	2	2.6	2	1.1
	No transplantation recorded	87	84.5	61	80.3	148	82.7
Number of rejections between 04-Apr-2009 and 01-Oct-2009	None	89	86.4	68	89.5	157	87.7
	At least one	14	13.6	8	10.5	22	12.3
Number of transplantation events between 01-Oct-2009 and 31-Oct-2010	0	89	86.4	65	85.5	154	86.0
	1	13	12.6	10	13.2	23	12.8
	2	1	1.0	1	1.3	2	1.1
Respiratory infection[s] between 01-Sep-2009 and 31-Oct-2010	No	103	100	74	97.4	177	98.9
	Yes	0	0.0	2	2.6	2	1.1
Acute bacterial infection[s] between 01-Sep-2009 and 31-Oct-2010	No	103	100	76	100	179	100
	Yes	0	0.0	0	0.0	0	0.0
Opportunistic infection[s] between 01-Sep-2009 and 31-Oct-2010	No	101	98.1	71	93.4	172	96.1
	Yes	2	1.9	5	6.6	7	3.9
Chronic viral infection[s] between 01-Oct-2008 and 31-Oct-2010	No	103	100	76	100	179	100
	Yes	0	0.0	0	0.0	0	0.0
Malignancy/cancer[s] between 01-Oct-2008 and 31-Oct-2010	No	97	94.2	67	88.2	164	91.6
	Yes	6	5.8	9	11.8	15	8.4
Reasons for end of follow-up	End of pandemic study period [31-Oct-2010]	92	89.3	72	94.7	164	91.6
	Death	6	5.8	3	3.9	9	5.0
	End of CRPD GOLD follow-up	5	4.9	1	1.3	6	3.4

nvac = no Pandemrix
vac = Pandemrix
**Each subject is classified in one category. All combinations are possible. Only transplantations between 04-Apr-2009 and 31-Oct-2010 are taken into account
n = number of subjects in a given category
Value = value of the considered parameter

% = n / Number of subjects with available results x 100
SD = Standard deviation

Table 16 Combinations of organs transplanted and rejected per case (Subset 1a)

		No Pandemrix N = 105		Pandemrix N = 79		Total N = 184	
Characteristics	Categories	n	%	n	%	n	%
Number of transplanted organs	0	87	82.9	61	77.2	148	80.4
	1	16	15.2	16	20.3	32	17.4
	2	2	1.9	2	2.5	4	2.2
Combinations of transplanted organs	Heart	0	0.0	1	5.6	1	2.8
	Kidney	10	55.6	9	50.0	19	52.8
	Kidney Liver	2	11.1	0	0.0	2	5.6
	Kidney Pancreas	0	0.0	2	11.1	2	5.6
	Liver	6	33.3	3	16.7	9	25.0
	Lung	0	0.0	2	11.1	2	5.6
	Pancreas	0	0.0	1	5.6	1	2.8
	No transplantation	87	-	61	-	148	-
Number of rejected organs	1	104	99.0	78	98.7	182	98.9
	2	1	1.0	1	1.3	2	1.1
Combinations of rejected organs	Heart	4	3.8	4	5.1	8	4.3
	Kidney	39	37.1	56	70.9	95	51.6
	Kidney Liver	1	1.0	0	0.0	1	0.5
	Kidney Pancreas	0	0.0	1	1.3	1	0.5
	Liver	11	10.5	7	8.9	18	9.8
	Lung	1	1.0	4	5.1	5	2.7
	Unspecified	49	46.7	7	8.9	56	30.4
Number of transplanted or rejected organs	1	103	98.1	76	96.2	179	97.3
	2	2	1.9	3	3.8	5	2.7
Combinations of transplanted or rejected organs	Heart	4	3.8	4	5.1	8	4.3
	Kidney	39	37.1	54	68.4	93	50.5
	Kidney Liver	2	1.9	0	0.0	2	1.1
	Kidney Pancreas	0	0.0	3	3.8	3	1.6
	Liver	10	9.5	7	8.9	17	9.2
	Lung	1	1.0	4	5.1	5	2.7
	Unspecified	49	46.7	7	8.9	56	30.4

N = number of subject
n = number of subject in a given category
% = n / Number of subject with available results x 100
Subjects with several organs transplanted or rejected:
Subject [redacted] had transplantations for Kidney and Liver, and rejections for Kidney and Liver
Subject [redacted] had transplantations for Kidney and Pancreas, and rejections for Kidney
Subject [redacted] had transplantations for Kidney and Liver, and rejections for Liver
Subject [redacted] had transplantations for Pancreas, and rejections for Kidney
Subject [redacted] had transplantations for Kidney and Pancreas, and rejections for Kidney and Pancreas
Note: Only transplantations and rejections between 04-Apr-2009 and 31-Oct-2010 are taken into account

Figure 5 Frequency of rejections per day after first dose of Pandemrix (Subset 1a)

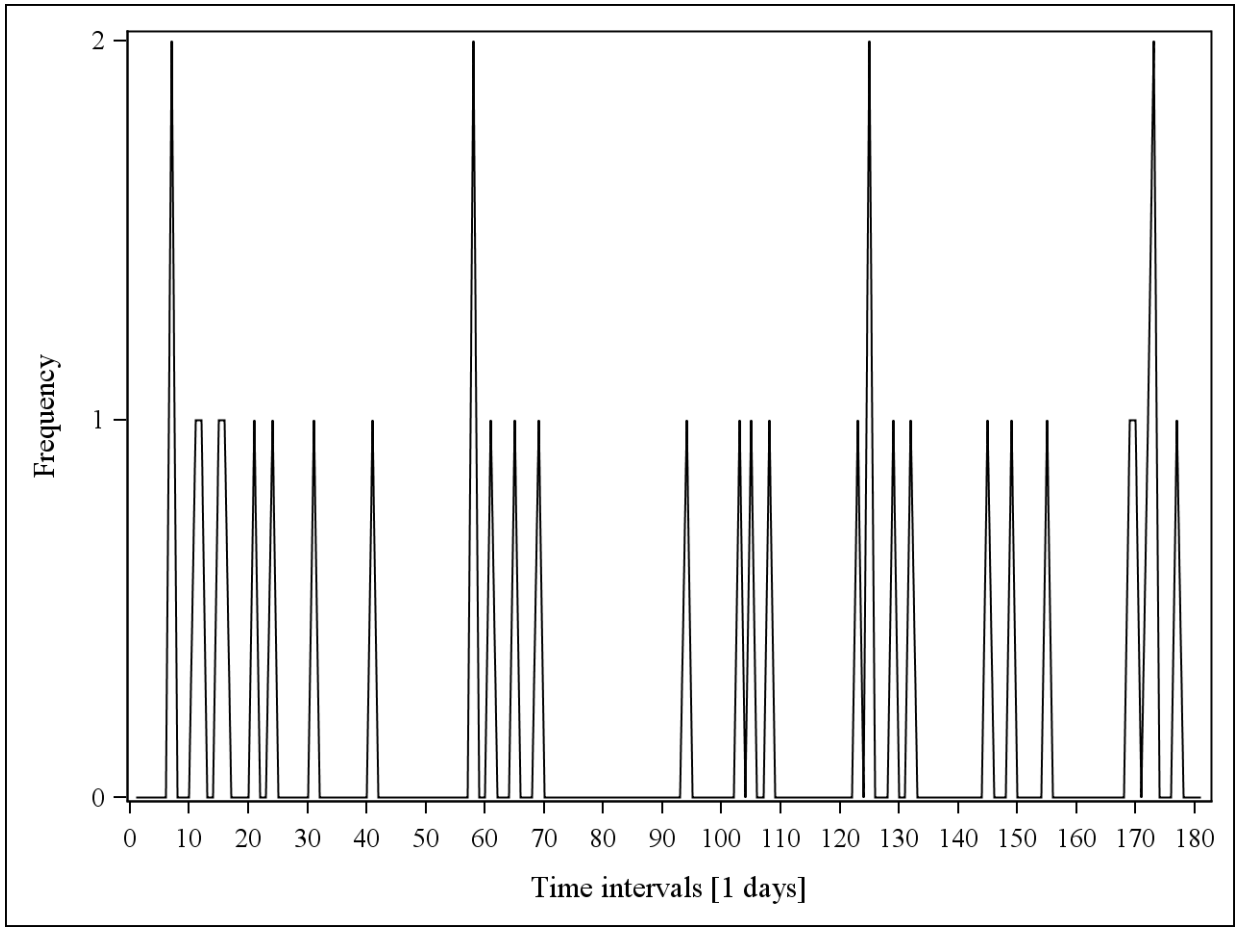

Figure 6 Frequency of rejections per week after first dose of Pandemrix (Subset 1a)

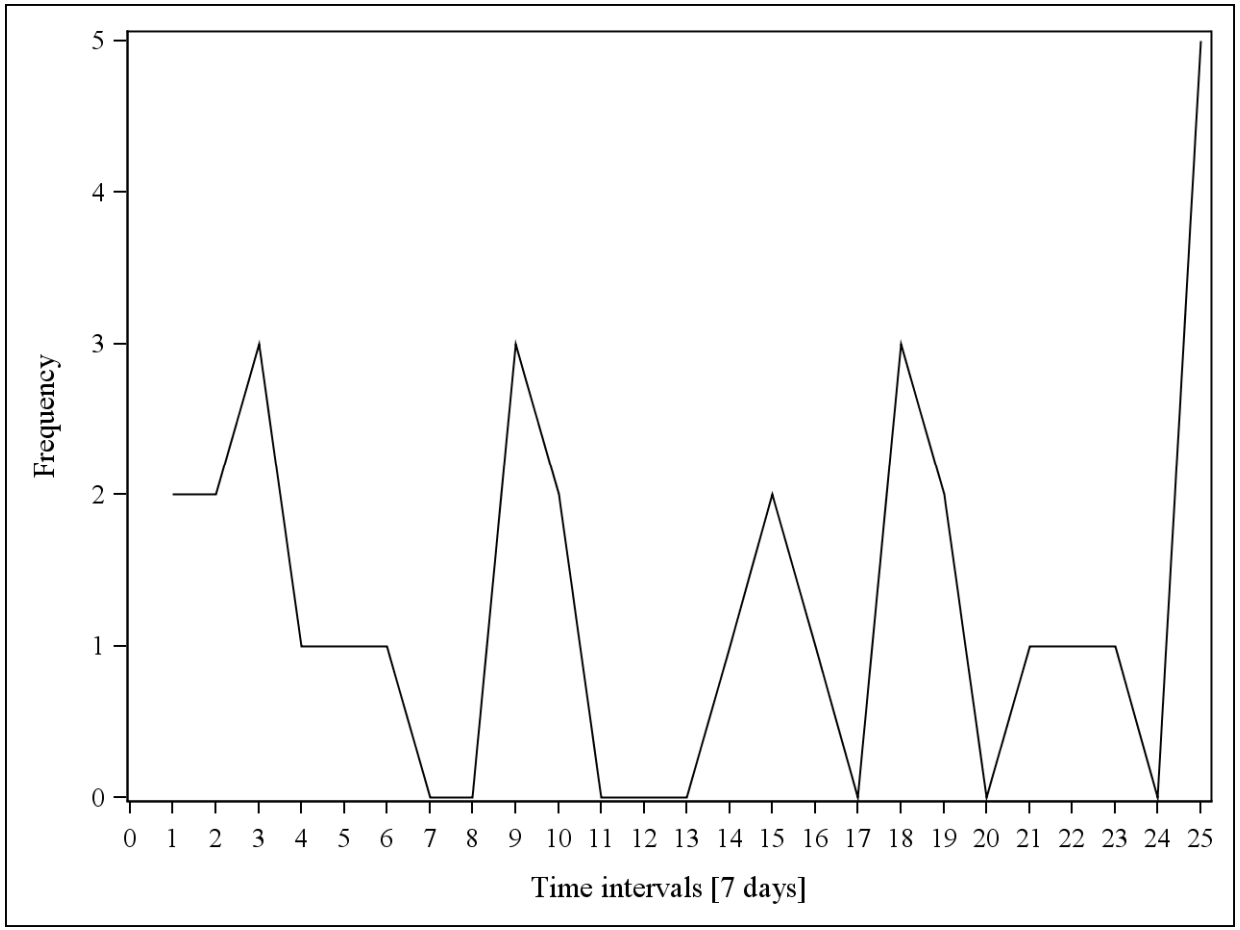

Table 17 Demographic and baseline characteristics (Subset 1b)

		nvac N = 36		vac N = 31		Total N = 67	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Age at 01-Oct-2009 [years]	N	36	-	31	-	67	-
	Mean	51.4	-	52.4	-	51.8	-
	SD	19.31	-	14.27	-	17.05	-
	Median	53.0	-	52.0	-	52.0	-
	Minimum	2	-	23	-	2	-
	Maximum	89	-	91	-	91	-
Age group at 01-Oct-2009 [years]	[0-17]	2	5.6	0	0.0	2	3.0
	[18-44]	7	19.4	10	32.3	17	25.4
	[45-60]	15	41.7	11	35.5	26	38.8
	61+	12	33.3	10	32.3	22	32.8
Gender	Female	20	55.6	10	32.3	30	44.8
	Male	16	44.4	21	67.7	37	55.2
Died between 01-Oct-2009 and 31-Oct-2010	No	33	91.7	28	90.3	61	91.0
	Yes	3	8.3	3	9.7	6	9.0
Time since transplantation at 01-Oct-2009 [days]	Before transplantation or more than 180 days after transplantation	36	100	25	80.6	61	91.0
	0-30	0	0.0	2	6.5	2	3.0
	31-90	0	0.0	0	0.0	0	0.0
	91-180	0	0.0	4	12.9	4	6.0
Organ transplanted before or during the season**	Heart	0	0.0	1	3.2	1	1.5
	Kidney	4	11.1	7	22.6	11	16.4
	Kidney+Liver	2	5.6	0	0.0	2	3.0
	Kidney+Pancreas	0	0.0	2	6.5	2	3.0
	Liver	3	8.3	2	6.5	5	7.5
	Lung	0	0.0	2	6.5	2	3.0
	No transplantation recorded	27	75.0	17	54.8	44	65.7
Number of rejections between 04-Apr-2009 and 01-Oct-2009	None	32	88.9	25	80.6	57	85.1
	At least one	4	11.1	6	19.4	10	14.9
Number of transplantation events between 01-Oct-2009 and 31-Oct-2010	0	27	75.0	22	71.0	49	73.1
	1	6	16.7	8	25.8	14	20.9
	2	2	5.6	1	3.2	3	4.5
	4	1	2.8	0	0.0	1	1.5
Respiratory infection[s] between 01-Sep-2009 and 31-Oct-2010	No	35	97.2	29	93.5	64	95.5
	Yes	1	2.8	2	6.5	3	4.5
Acute bacterial infection[s] between 01-Sep-2009 and 31-Oct-2010	No	36	100	31	100	67	100
	Yes	0	0.0	0	0.0	0	0.0
Opportunistic infection[s] between 01-Sep-2009 and 31-Oct-2010	No	35	97.2	27	87.1	62	92.5
	Yes	1	2.8	4	12.9	5	7.5
Chronic viral infection[s] between 01-Oct-2008 and 31-Oct-2010	No	36	100	31	100	67	100
	Yes	0	0.0	0	0.0	0	0.0

		nvac N = 36		vac N = 31		Total N = 67	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Malignancy/cancer[s] between 01-Oct-2008 and 31-Oct-2010	No	35	97.2	30	96.8	65	97.0
	Yes	1	2.8	1	3.2	2	3.0
Chemotherapy between 01-Oct-2008 and 31-Oct-2010	No	30	83.3	29	93.5	59	88.1
	Yes	6	16.7	2	6.5	8	11.9
Reasons for end of follow-up	End of pandemic study period [31-Oct-2010]	32	88.9	28	90.3	60	89.6
	Death	3	8.3	3	9.7	6	9.0
	End of CRPD GOLD follow-up	1	2.8	0	0.0	1	1.5

nvac = no Pandemrix
vac = Pandemrix
**Each subject is classified in one category. All combinations are possible. Only transplantations between 04-Apr-2009 and 31-Oct-2010 are taken into account
n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD = Standard deviation

Table 18 Demographic and baseline characteristics (Subset 1b, subjects with transplantation or rejection for only one organ)

		nvac N = 34		vac N = 29		Total N = 63	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Age at 01-Oct-2009 [years]	N	34	-	29	-	63	-
	Mean	52.3	-	53.4	-	52.8	-
	SD	18.99	-	14.15	-	16.81	-
	Median	54.0	-	53.0	-	53.0	-
	Minimum	2	-	23	-	2	-
	Maximum	89	-	91	-	91	-
Age group at 01-Oct-2009 [years]	[0-17]	2	5.9	0	0.0	2	3.2
	[18-44]	6	17.6	8	27.6	14	22.2
	[45-60]	14	41.2	11	37.9	25	39.7
	61+	12	35.3	10	34.5	22	34.9
Gender	Female	19	55.9	9	31.0	28	44.4
	Male	15	44.1	20	69.0	35	55.6
Died between 01-Oct-2009 and 31-Oct-2010	No	31	91.2	27	93.1	58	92.1
	Yes	3	8.8	2	6.9	5	7.9
Time since transplantation at 01-Oct-2009 [days]	Before transplantation or more than 180 days after transplantation	34	100	25	86.2	59	93.7
	0-30	0	0.0	2	6.9	2	3.2
	31-90	0	0.0	0	0.0	0	0.0
	91-180	0	0.0	2	6.9	2	3.2
Organ transplanted before or during the season**	Heart	0	0.0	1	3.4	1	1.6
	Kidney	4	11.8	7	24.1	11	17.5
	Liver	3	8.8	2	6.9	5	7.9
	Lung	0	0.0	2	6.9	2	3.2
	No transplantation recorded	27	79.4	17	58.6	44	69.8
Number of rejections between 04-Apr-2009 and 01-Oct-2009	None	30	88.2	24	82.8	54	85.7
	At least one	4	11.8	5	17.2	9	14.3
Number of transplantation events between 01-Oct-2009 and 31-Oct-2010	0	27	79.4	20	69.0	47	74.6
	1	6	17.6	8	27.6	14	22.2
	2	1	2.9	1	3.4	2	3.2
Respiratory infection[s] between 01-Sep-2009 and 31-Oct-2010	No	33	97.1	27	93.1	60	95.2
	Yes	1	2.9	2	6.9	3	4.8
Acute bacterial infection[s] between 01-Sep-2009 and 31-Oct-2010	No	34	100	29	100	63	100
	Yes	0	0.0	0	0.0	0	0.0
Opportunistic infection[s] between 01-Sep-2009 and 31-Oct-2010	No	33	97.1	26	89.7	59	93.7
	Yes	1	2.9	3	10.3	4	6.3
Chronic viral infection[s] between 01-Oct-2008 and 31-Oct-2010	No	34	100	29	100	63	100
	Yes	0	0.0	0	0.0	0	0.0
Malignancy/cancer[s] between 01-Oct-2008 and 31-Oct-2010	No	33	97.1	28	96.6	61	96.8
	Yes	1	2.9	1	3.4	2	3.2
Chemotherapy between 01-Oct-2008 and 31-Oct-2010	No	29	85.3	27	93.1	56	88.9
	Yes	5	14.7	2	6.9	7	11.1
Reasons for end of follow-up	End of pandemic study period [31-Oct-2010]	30	88.2	27	93.1	57	90.5
	Death	3	8.8	2	6.9	5	7.9
	End of CRPD GOLD follow-up	1	2.9	0	0.0	1	1.6

nvac = no Pandemrix
vac = Pandemrix
**Each subject is classified in one category. All combinations are possible. Only transplantations between 04-Apr-2009 and 31-Oct-2010 are taken into account

n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD = Standard deviation

Table 19 Combinations of organs transplanted and rejected per case (Subset 1b)

		No Pandemrix N = 36		Pandemrix N = 31		Total N = 67	
Characteristics	Categories	n	%	n	%	n	%
Number of transplanted organs	0	27	75.0	17	54.8	44	65.7
	1	7	19.4	12	38.7	19	28.4
	2	2	5.6	2	6.5	4	6.0
Combinations of transplanted organs	Heart	0	0.0	1	7.1	1	4.3
	Kidney	4	44.4	7	50.0	11	47.8
	Kidney Liver	2	22.2	0	0.0	2	8.7
	Kidney Pancreas	0	0.0	2	14.3	2	8.7
	Liver	3	33.3	2	14.3	5	21.7
	Lung	0	0.0	2	14.3	2	8.7
	No transplantation	27	-	17	-	44	-
Number of rejected organs	1	35	97.2	30	96.8	65	97.0
	2	1	2.8	1	3.2	2	3.0
Combinations of rejected organs	Heart	1	2.8	2	6.5	3	4.5
	Kidney	12	33.3	20	64.5	32	47.8
	Kidney Liver	1	2.8	0	0.0	1	1.5
	Kidney Pancreas	0	0.0	1	3.2	1	1.5
	Liver	6	16.7	4	12.9	10	14.9
	Lung	1	2.8	3	9.7	4	6.0
	Unspecified	15	41.7	1	3.2	16	23.9
Number of transplanted or rejected organs	1	34	94.4	29	93.5	63	94.0
	2	2	5.6	2	6.5	4	6.0
Combinations of transplanted or rejected organs	Heart	1	2.8	2	6.5	3	4.5
	Kidney	12	33.3	19	61.3	31	46.3
	Kidney Liver	2	5.6	0	0.0	2	3.0
	Kidney Pancreas	0	0.0	2	6.5	2	3.0
	Liver	5	13.9	4	12.9	9	13.4
	Lung	1	2.8	3	9.7	4	6.0
	Unspecified	15	41.7	1	3.2	16	23.9

N = number of subject
n = number of subject in a given category
% = n / Number of subject with available results x 100
Subjects with several organs transplanted or rejected:
Subject [redacted] had transplantations for Kidney and Liver, and rejections for Kidney and Liver
Subject [redacted] had transplantations for Kidney and Pancreas, and rejections for Kidney
Subject [redacted] had transplantations for Kidney and Liver, and rejections for Liver
Subject [redacted] had transplantations for Kidney and Pancreas, and rejections for Kidney and Pancreas
Note: Only transplantations and rejections between 04-Apr-2009 and 31-Oct-2010 are taken into account

Table 20 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix and the time since transplantation (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	184	100.0	245	70378
Data after censoring according to transplantations	184	100.0	244	65276
Data after censoring according to second rejection	184	100.0	184	59836
Subjects with at least one exposure of interest (Pandemrix, transplantation)	91	49.5	91	27627
Pandemrix - Control period before first dose	91	49.5	35	8193
Pandemrix - Risk period after dose 1	71	38.6	8	2069
Pandemrix - Control period after dose 1	55	29.9	35	12748
Pandemrix - Risk period after dose 2	16	8.7	1	496
Pandemrix - Control period after dose 2	16	8.7	12	4121
Pandemrix - Pooled risk periods	71	38.6	9	2565
Pandemrix - Pooled control periods	91	49.5	82	25062
Day0 to Day30 after transplantation	23	12.5	10	640
Day31 to Day90 after transplantation	24	13.0	8	1154
Day91 to Day180 after transplantation	21	11.4	2	1668
> 180 days after transplantation	80	43.5	71	24165

Figure 7 Frequency of rejections per day after transplantation (Subset 1a)

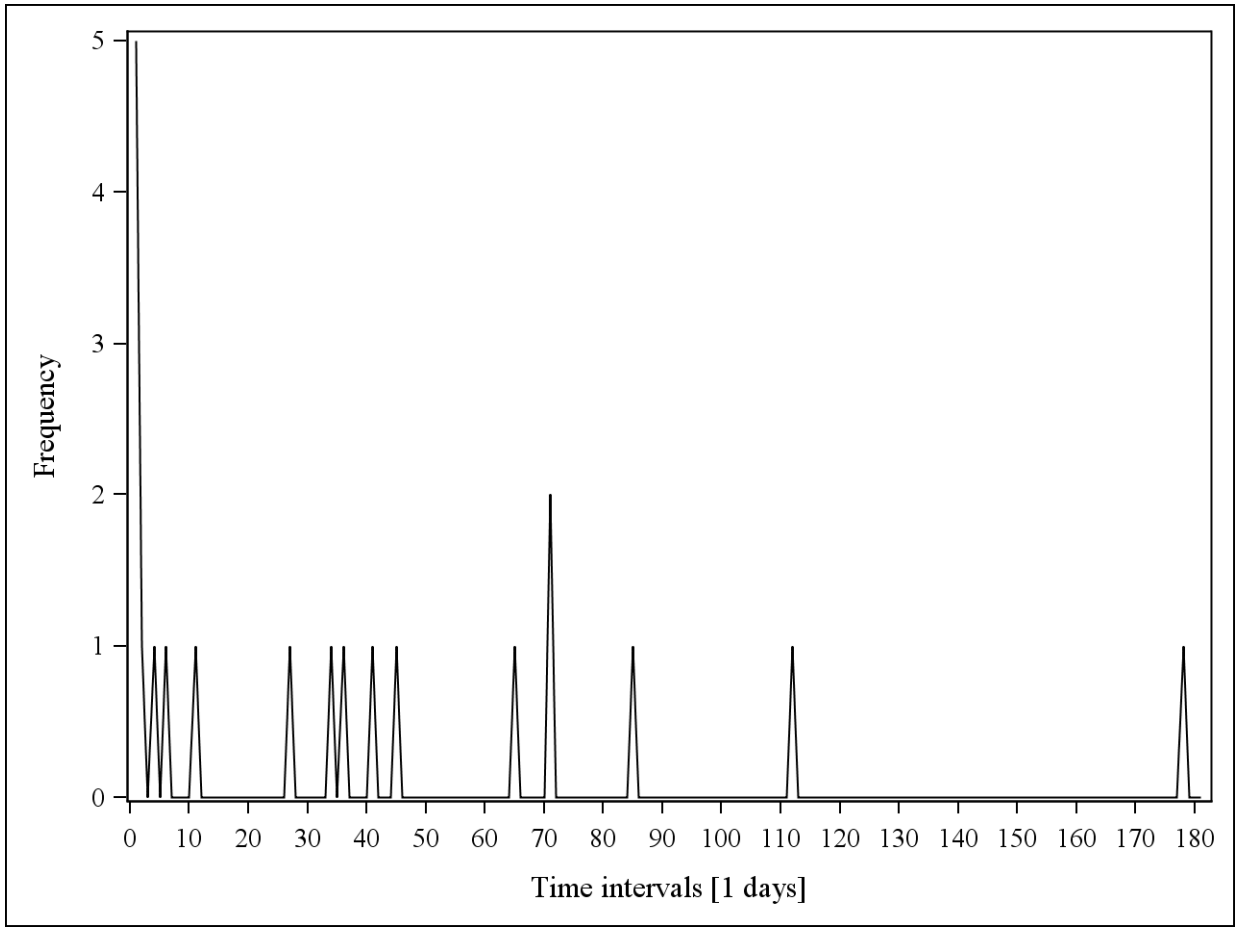

Figure 8 Frequency of rejections per week after transplantation (Subset 1a)

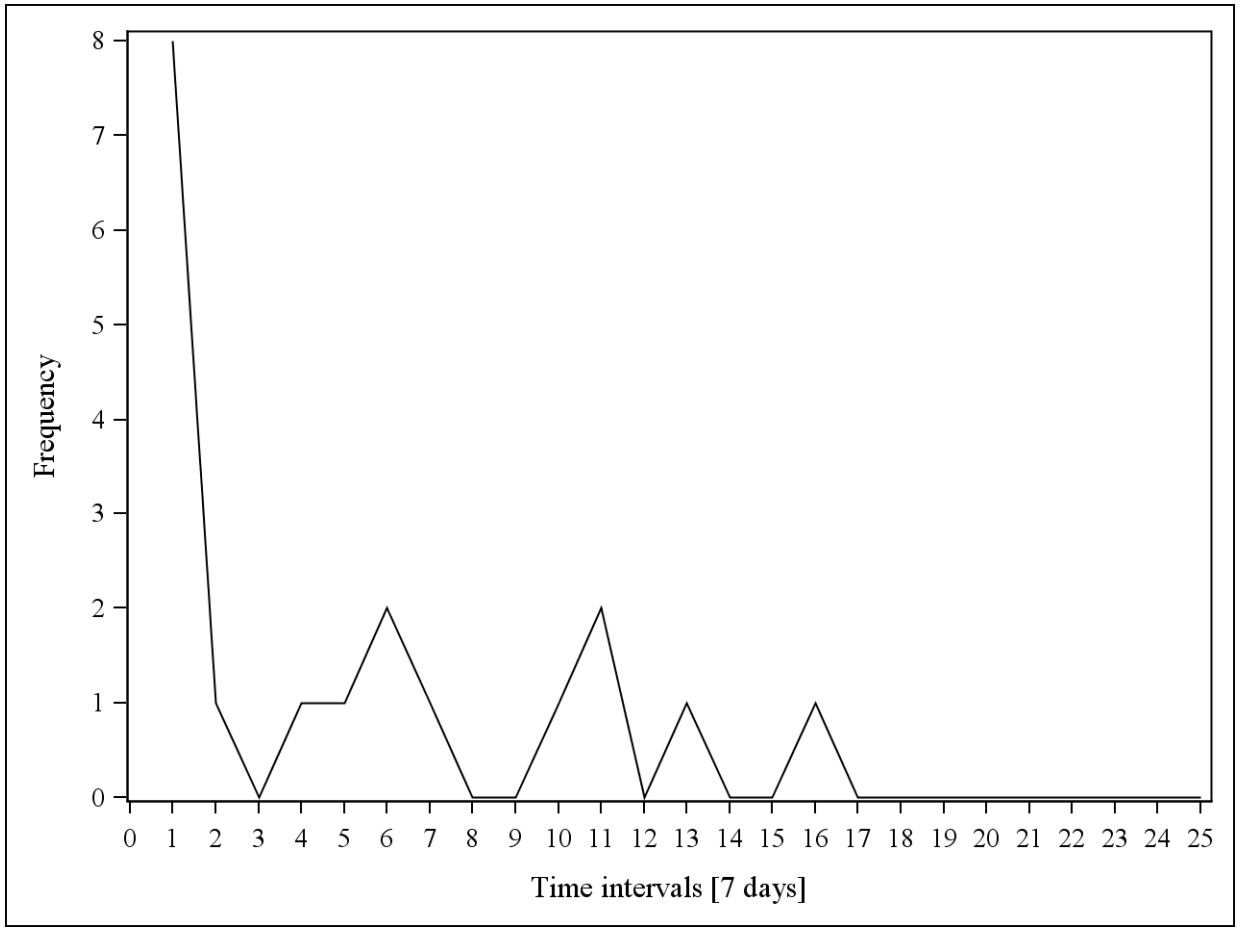

Figure 9 Frequency of rejections per month after transplantation (Subset 1a)

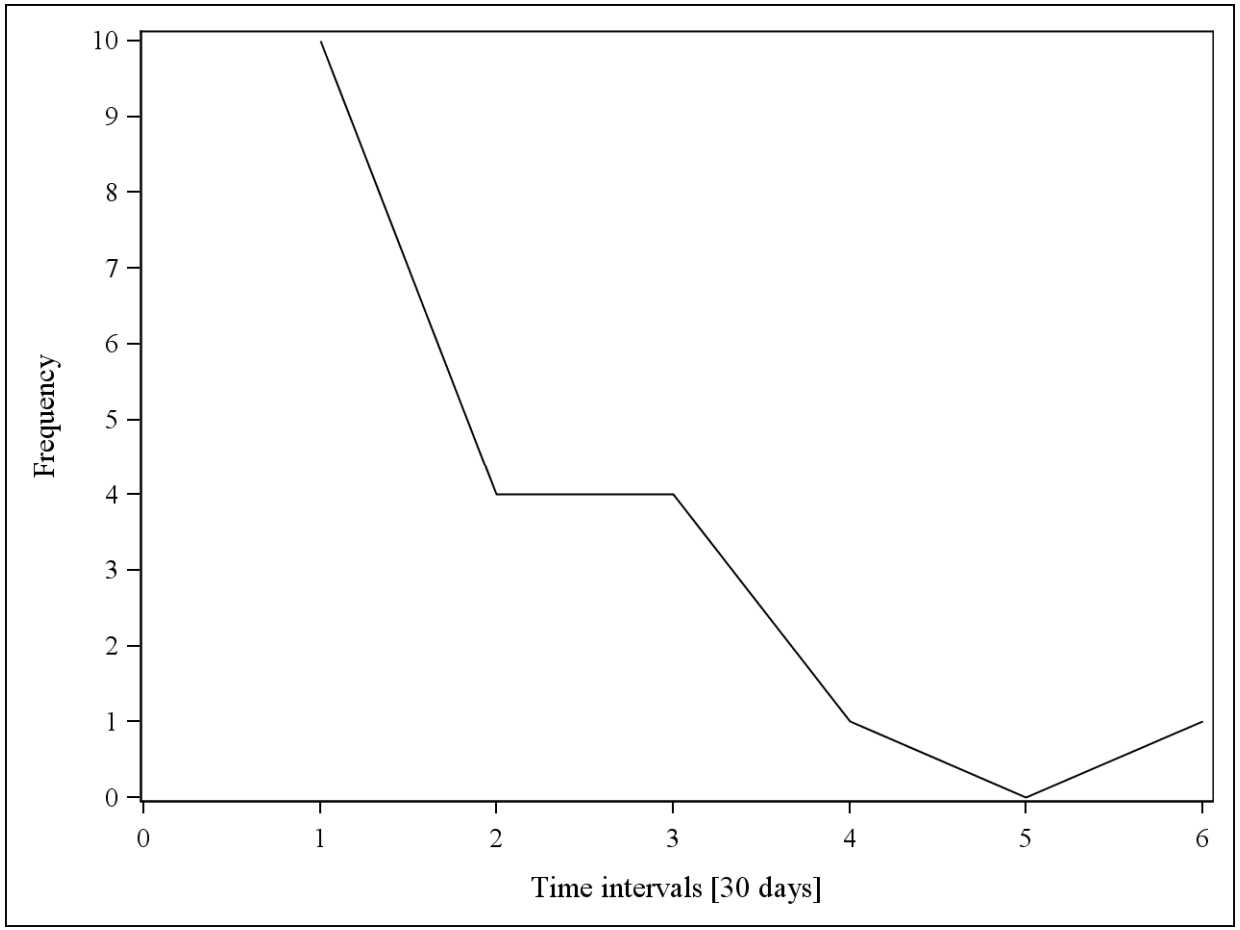

Figure 10 Frequency of rejections by week (Subset 1a)

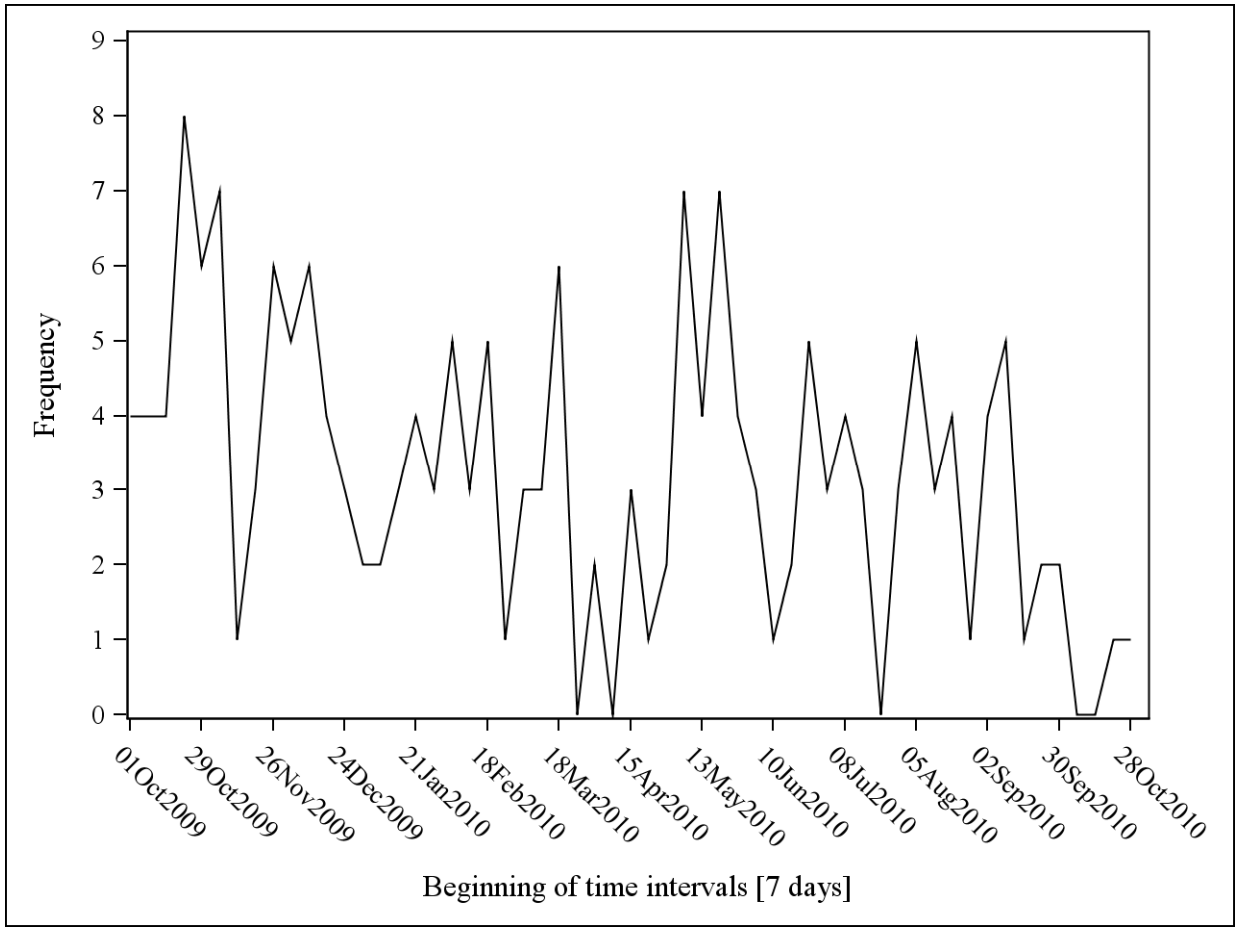

Figure 11 Frequency of rejections by month (Subset 1a)

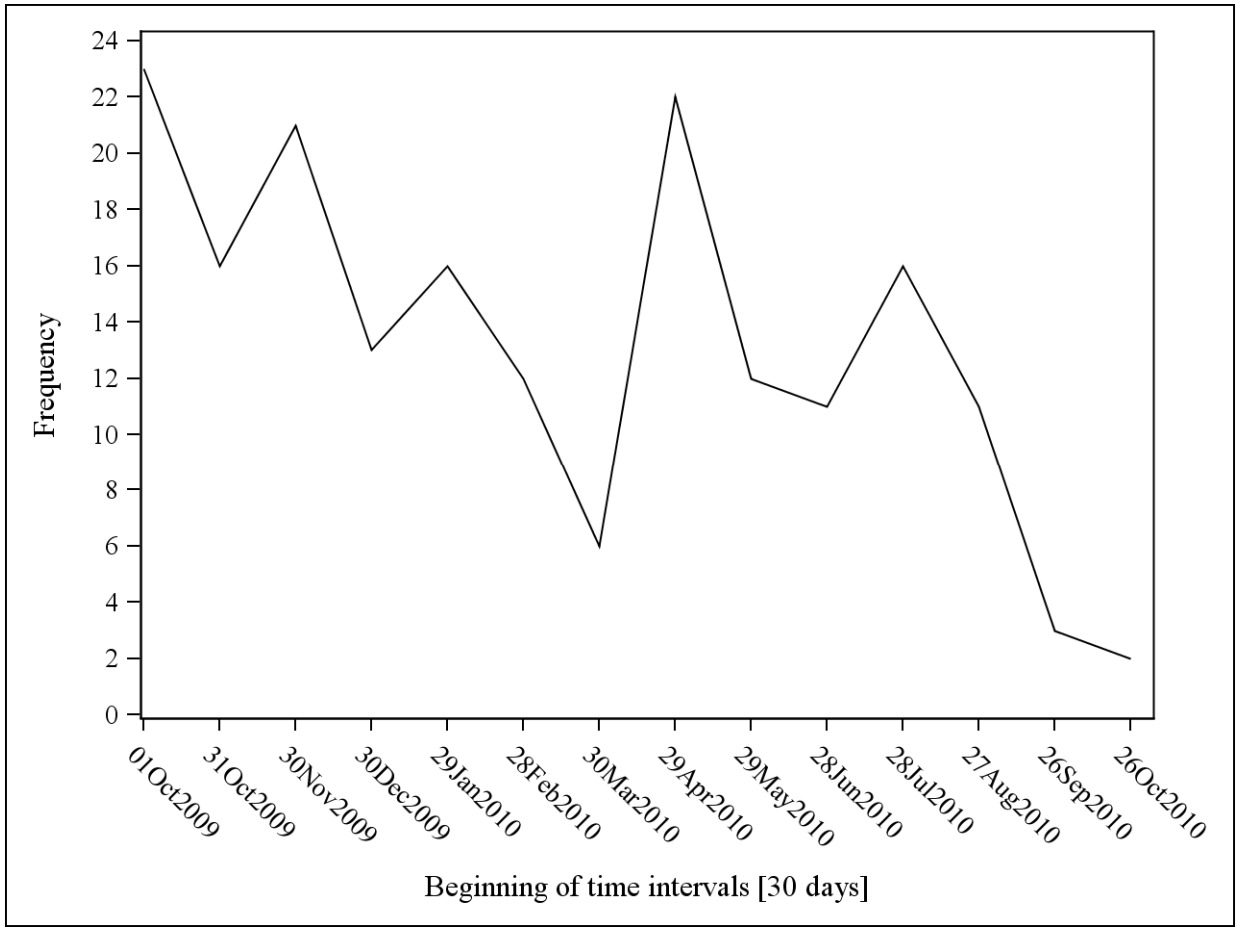

Table 21 Relative incidence of SOT rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	30 days after any dose vs. other periods	1.05	0.52	2.14
Time since transplantation	0-30 vs. >180 days	4.14	0.91	18.82
	31-90 vs. >180 days	2.25	0.54	9.44
	91-180 vs. >180 days	0.37	0.06	2.31

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 22 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and seasonal vaccination (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	184	100.0	245	70378
Data after censoring according to transplantations	184	100.0	244	65276
Data after censoring according to second rejection	184	100.0	184	59836
Subjects with at least one exposure of interest (Pandemrix, Seasonal vaccine, transplantation)	119	64.7	119	37100
Pandemrix - Control period before first dose	119	64.7	63	17666
Pandemrix - Risk period after dose 1	71	38.6	8	2069
Pandemrix - Control period after dose 1	55	29.9	35	12748
Pandemrix - Risk period after dose 2	16	8.7	1	496
Pandemrix - Control period after dose 2	16	8.7	12	4121
Pandemrix - Pooled risk periods	71	38.6	9	2565
Pandemrix - Pooled control periods	119	64.7	110	34535
Day0 to Day30 after transplantation	23	12.5	10	640
Day31 to Day90 after transplantation	24	13.0	8	1154
Day91 to Day180 after transplantation	21	11.4	2	1668
> 180 days after transplantation	108	58.7	99	33638
Day0 to Day30 after Seasonal vaccine	94	51.1	6	3358
> 30 days after Seasonal vaccine	119	64.7	113	33742

Table 23 Relative incidence of SOT rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and seasonal vaccination (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	30 days after any dose vs. other periods	1.17	0.57	2.39
Time since transplantation	0-30 vs. >180 days	4.19	0.89	19.69
	31-90 vs. >180 days	2.26	0.52	9.91
	91-180 vs. >180 days	0.37	0.06	2.49
Seasonal influenza vaccination	30 days after vaccination vs. other periods	0.44	0.18	1.05

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 24 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and respiratory infections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	184	100.0	245	70378
Data after censoring according to transplantations	184	100.0	244	65276
Data after censoring according to second rejection	184	100.0	184	59836
Subjects with at least one exposure of interest (Pandemrix, Respiratory infection, transplantation)	91	49.5	91	27627
Pandemrix - Control period before first dose	91	49.5	35	8193
Pandemrix - Risk period after dose 1	71	38.6	8	2069
Pandemrix - Control period after dose 1	55	29.9	35	12748
Pandemrix - Risk period after dose 2	16	8.7	1	496
Pandemrix - Control period after dose 2	16	8.7	12	4121
Pandemrix - Pooled risk periods	71	38.6	9	2565
Pandemrix - Pooled control periods	91	49.5	82	25062
Day0 to Day30 after transplantation	23	12.5	10	640
Day31 to Day90 after transplantation	24	13.0	8	1154
Day91 to Day180 after transplantation	21	11.4	2	1668
> 180 days after transplantation	80	43.5	71	24165
Day0 to Day30 after Respiratory infection	2	1.1	0	62
> 30 days after Respiratory infection	91	49.5	91	27565

Table 25 Relative incidence of SOT rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and respiratory infections (Subset 1a)

No records exist in this table

Table 26 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and opportunistic infections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	184	100.0	245	70378
Data after censoring according to transplantations	184	100.0	244	65276
Data after censoring according to second rejection	184	100.0	184	59836
Subjects with at least one exposure of interest (Opportunistic infection, Pandemrix, transplantation)	92	50.0	92	28023
Pandemrix - Control period before first dose	92	50.0	36	8589
Pandemrix - Risk period after dose 1	71	38.6	8	2069
Pandemrix - Control period after dose 1	55	29.9	35	12748
Pandemrix - Risk period after dose 2	16	8.7	1	496
Pandemrix - Control period after dose 2	16	8.7	12	4121
Pandemrix - Pooled risk periods	71	38.6	9	2565
Pandemrix - Pooled control periods	92	50.0	83	25458
Day0 to Day30 after transplantation	23	12.5	10	640
Day31 to Day90 after transplantation	24	13.0	8	1154
Day91 to Day180 after transplantation	21	11.4	2	1668
> 180 days after transplantation	81	44.0	72	24561
Day0 to Day30 after Opportunistic infection	6	3.3	1	260
> 30 days after Opportunistic infection	92	50.0	91	27763

Table 27 Relative incidence of SOT rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and opportunistic infections (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	30 days after any dose vs. other periods	1.06	0.52	2.15
Time since transplantation	0-30 vs. >180 days	4.03	0.87	18.71
	31-90 vs. >180 days	2.22	0.52	9.52
	91-180 vs. >180 days	0.36	0.06	2.29
Opportunistic infections	30 days after infection vs. other periods	1.75	0.17	18.39

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 28 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and acute bacterial infections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	184	100.0	245	70378
Data after censoring according to transplantations	184	100.0	244	65276
Data after censoring according to second rejection	184	100.0	184	59836
Subjects with at least one exposure of interest (Acute bacterial infection, Pandemrix, transplantation)	91	49.5	91	27627
Pandemrix - Control period before first dose	91	49.5	35	8193
Pandemrix - Risk period after dose 1	71	38.6	8	2069
Pandemrix - Control period after dose 1	55	29.9	35	12748
Pandemrix - Risk period after dose 2	16	8.7	1	496
Pandemrix - Control period after dose 2	16	8.7	12	4121
Pandemrix - Pooled risk periods	71	38.6	9	2565
Pandemrix - Pooled control periods	91	49.5	82	25062
Day0 to Day30 after transplantation	23	12.5	10	640
Day31 to Day90 after transplantation	24	13.0	8	1154
Day91 to Day180 after transplantation	21	11.4	2	1668
> 180 days after transplantation	80	43.5	71	24165
> 30 days after Acute bacterial infection	91	49.5	91	27627

Table 29 Relative incidence of SOT rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and acute bacterial infections (Subset 1a)

No records exist in this table

Table 30 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and chronic viral infections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	178	100.0	239	68002
Data after censoring according to transplantations	178	100.0	238	62976
Data after censoring according to second rejection	178	100.0	178	57536
Subjects with at least one exposure of interest (Chronic viral infection, Pandemrix, transplantation)	88	49.4	88	26515
Pandemrix - Control period before first dose	88	49.4	33	7430
Pandemrix - Risk period after dose 1	70	39.3	8	2038
Pandemrix - Control period after dose 1	54	30.3	34	12430
Pandemrix - Risk period after dose 2	16	9.0	1	496
Pandemrix - Control period after dose 2	16	9.0	12	4121
Pandemrix - Pooled risk periods	70	39.3	9	2534
Pandemrix - Pooled control periods	88	49.4	79	23981
Day0 to Day30 after transplantation	21	11.8	9	603
Day31 to Day90 after transplantation	22	12.4	7	1034
Day91 to Day180 after transplantation	19	10.7	2	1488
> 180 days after transplantation	77	43.3	70	23390
> 365 days after Chronic viral infection	88	49.4	88	26515

Table 31 Relative incidence of SOT rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and chronic viral infection (Subset 1a)

No records exist in this table

Table 32 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risks period of Pandemrix the time since transplantation and malignancies/cancers (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	178	100.0	239	68002
Data after censoring according to transplantations	178	100.0	238	62976
Data after censoring according to second rejection	178	100.0	178	57536
Subjects with at least one exposure of interest (Cancer, Pandemrix, transplantation)	93	52.2	93	28376
Pandemrix - Control period before first dose	93	52.2	38	9291
Pandemrix - Risk period after dose 1	70	39.3	8	2038
Pandemrix - Control period after dose 1	54	30.3	34	12430
Pandemrix - Risk period after dose 2	16	9.0	1	496
Pandemrix - Control period after dose 2	16	9.0	12	4121
Pandemrix - Pooled risk periods	70	39.3	9	2534
Pandemrix - Pooled control periods	93	52.2	84	25842
Day0 to Day30 after transplantation	21	11.8	9	603
Day31 to Day90 after transplantation	22	12.4	7	1034
Day91 to Day180 after transplantation	19	10.7	2	1488
> 180 days after transplantation	82	46.1	75	25251
Day0 to Day365 after Cancer	15	8.4	11	3103
> 365 days after Cancer	93	52.2	82	25273

Table 33 Relative incidence of SOT rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and malignancies/cancers (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	30 days after any dose vs. other periods	1.13	0.56	2.30
Time since transplantation	0-30 vs. >180 days	2.51	0.51	12.25
	31-90 vs. >180 days	1.46	0.32	6.61
	91-180 vs. >180 days	0.30	0.04	2.08
Malignancies/ cancers	365 days after any record vs. other periods	3.50	0.86	14.15

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 34 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risks period of Pandemrix the time since transplantation and all covariates (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	178	100.0	239	68002
Data after censoring according to transplantations	178	100.0	238	62976
Data after censoring according to second rejection	178	100.0	178	57536
Subjects with at least one exposure of interest (Acute bacterial infection, Cancer, Chronic viral infection, Opportunistic infection, Pandemrix, Respiratory infection, Seasonal vaccine, transplantation)	120	67.4	120	37453
Pandemrix - Control period before first dose	120	67.4	65	18368
Pandemrix - Risk period after dose 1	70	39.3	8	2038
Pandemrix - Control period after dose 1	54	30.3	34	12430
Pandemrix - Risk period after dose 2	16	9.0	1	496
Pandemrix - Control period after dose 2	16	9.0	12	4121
Pandemrix - Pooled risk periods	70	39.3	9	2534
Pandemrix - Pooled control periods	120	67.4	111	34919
Day0 to Day30 after transplantation	21	11.8	9	603
Day31 to Day90 after transplantation	22	12.4	7	1034
Day91 to Day180 after transplantation	19	10.7	2	1488
> 180 days after transplantation	109	61.2	102	34328
Day0 to Day30 after Seasonal vaccine	92	51.7	5	3273
> 30 days after Seasonal vaccine	120	67.4	115	34180
Day0 to Day30 after Respiratory infection	2	1.1	0	62
> 30 days after Respiratory infection	120	67.4	120	37391
Day0 to Day30 after Opportunistic infection	6	3.4	1	260
> 30 days after Opportunistic infection	120	67.4	119	37193
> 30 days after Acute bacterial infection	120	67.4	120	37453
> 365 days after Chronic viral infection	120	67.4	120	37453
Day0 to Day365 after Cancer	15	8.4	11	3103
> 365 days after Cancer	120	67.4	109	34350

Table 35 Relative incidence of SOT rejection within 30 days after Pandemrix vaccination adjusted for all covariates (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	30 days after any dose vs. other periods	1.29	0.63	2.63
Time since transplantation	0-30 vs. >180 days	2.45	0.48	12.44
	31-90 vs. >180 days	1.42	0.30	6.74
	91-180 vs. >180 days	0.30	0.04	2.24
Seasonal influenza vaccination	30 days after vaccination vs. other periods	0.38	0.15	0.98
Opportunistic infections	30 days after infection vs. other periods	1.82	0.17	19.24
Malignancies/ cancers	365 days after any record vs. other periods	3.36	0.83	13.66

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 36 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix and the time since transplantation – with subsequent rejections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	184	100.0	245	70378
Data after censoring according to transplantations	184	100.0	244	65276
Subjects with at least one exposure of interest (Pandemrix, transplantation)	91	49.5	129	31130
Pandemrix - Control period before first dose	91	49.5	43	8592
Pandemrix - Risk period after any dose	72	39.1	11	2655
Pandemrix - Control period after any dose	72	39.1	75	19883
Pandemrix - Pooled risk periods	72	39.1	11	2655
Pandemrix - Pooled control periods	91	49.5	118	28475
Day0 to Day30 after transplantation	23	12.5	10	640
Day31 to Day90 after transplantation	24	13.0	11	1238
Day91 to Day180 after transplantation	23	12.5	2	1776
> 180 days after transplantation	81	44.0	106	27476

Table 37 Relative incidence of SOT rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation - not accounting for perturbed post-event exposure (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	30 days after any dose vs. other periods	1.11	0.59	2.09
Time since transplantation	0-30 vs. >180 days	2.14	0.71	6.43
	31-90 vs. >180 days	1.46	0.53	3.97
	91-180 vs. >180 days	0.23	0.05	1.05

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit

Table 38 Relative incidence of SOT rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and conditioned to previous rejections (Subset 1a)

No records exist in this table

Table 39 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of *Pandemrix* and the time since transplantation - subjects without previous rejections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	82	100.0	111	31597
Data after censoring according to transplantations	82	100.0	111	27771
Data after censoring according to second rejection	82	100.0	82	25425
Subjects with at least one exposure of interest (Pandemrix, transplantation)	82	100.0	82	25425
Pandemrix - Control period before first dose	82	100.0	32	7582
Pandemrix - Risk period after dose 1	62	75.6	7	1801
Pandemrix - Control period after dose 1	48	58.5	31	11625
Pandemrix - Risk period after dose 2	15	18.3	1	465
Pandemrix - Control period after dose 2	15	18.3	11	3952
Pandemrix - Pooled risk periods	62	75.6	8	2266
Pandemrix - Pooled control periods	82	100.0	74	23159
Day0 to Day30 after transplantation	21	25.6	10	614
Day31 to Day90 after transplantation	22	26.8	8	1034
Day91 to Day180 after transplantation	17	20.7	1	1316
> 180 days after transplantation	71	86.6	63	22461

Table 40 Relative incidence of SOT rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation - Subjects without previous rejections (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	30 days after any dose vs. other periods	1.02	0.48	2.13
Time since transplantation	0-30 vs. >180 days	4.80	0.82	28.10
	31-90 vs. >180 days	2.68	0.50	14.51
	91-180 vs. >180 days	0.19	0.02	1.91

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 41 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and previous rejection - Subjects with previous rejections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	9	100.0	18	3495
Data after censoring according to transplantations	9	100.0	18	3359
Data after censoring according to second rejection	9	100.0	9	2202
Subjects with at least one exposure of interest (Pandemrix, Previous rejection, transplantation)	9	100.0	9	2202
Pandemrix - Control period before first dose	9	100.0	3	611
Pandemrix - Risk period after dose 1	9	100.0	1	268
Pandemrix - Control period after dose 1	7	77.8	4	1123
Pandemrix - Risk period after dose 2	1	11.1	0	31
Pandemrix - Control period after dose 2	1	11.1	1	169
Pandemrix - Pooled risk periods	9	100.0	1	299
Pandemrix - Pooled control periods	9	100.0	8	1903
Day0 to Day30 after transplantation	2	22.2	0	26
Day31 to Day90 after transplantation	2	22.2	0	120
Day91 to Day180 after transplantation	4	44.4	1	352
> 180 days after transplantation	9	100.0	8	1704
Day0 to Day180 after Previous rejection	9	100.0	5	927
> 180 days after Previous rejection	6	66.7	4	1275

Table 42 Relative incidence of SOT rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and previous rejection - Subjects with previous rejections (Subset 1a)

No records exist in this table

Table 43 Heart transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix and the time since transplantation (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	8	100.0	9	2953
Data after censoring according to transplantations	8	100.0	9	2803
Data after censoring according to second rejection	8	100.0	8	2703
Subjects with at least one exposure of interest (Pandemrix, transplantation)	4	50.0	4	1219
Pandemrix - Control period before first dose	4	50.0	1	215
Pandemrix - Risk period after dose 1	4	50.0	0	124
Pandemrix - Control period after dose 1	4	50.0	3	880
Pandemrix - Pooled risk periods	4	50.0	0	124
Pandemrix - Pooled control periods	4	50.0	4	1095
> 180 days after transplantation	4	50.0	4	1219

Table 44 Kidney transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix and the time since transplantation (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	97	100.0	145	36917
Data after censoring according to transplantations	97	100.0	145	33766
Data after censoring according to second rejection	97	100.0	97	29510
Subjects with at least one exposure of interest (Pandemrix, transplantation)	65	67.0	65	19565
Pandemrix - Control period before first dose	65	67.0	24	5478
Pandemrix - Risk period after dose 1	53	54.6	5	1545
Pandemrix - Control period after dose 1	41	42.3	26	9049
Pandemrix - Risk period after dose 2	12	12.4	1	372
Pandemrix - Control period after dose 2	12	12.4	9	3121
Pandemrix - Pooled risk periods	53	54.6	6	1917
Pandemrix - Pooled control periods	65	67.0	59	17648
Day0 to Day30 after transplantation	15	15.5	6	425
Day31 to Day90 after transplantation	16	16.5	5	744
Day91 to Day180 after transplantation	14	14.4	2	1110
> 180 days after transplantation	58	59.8	52	17286

Table 45 Relative incidence of kidney transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	30 days after any dose vs. other periods	0.85	0.38	1.90
Time since transplantation	0-30 vs. >180 days	3.73	0.52	26.53
	31-90 vs. >180 days	2.68	0.42	16.95
	91-180 vs. >180 days	0.74	0.08	6.69

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 46 Kidney transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and seasonal vaccination (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	97	100.0	145	36917
Data after censoring according to transplantations	97	100.0	145	33766
Data after censoring according to second rejection	97	100.0	97	29510
Subjects with at least one exposure of interest (Pandemrix, Seasonal vaccine, transplantation)	73	75.3	73	22135
Pandemrix - Control period before first dose	73	75.3	32	8048
Pandemrix - Risk period after dose 1	53	54.6	5	1545
Pandemrix - Control period after dose 1	41	42.3	26	9049
Pandemrix - Risk period after dose 2	12	12.4	1	372
Pandemrix - Control period after dose 2	12	12.4	9	3121
Pandemrix - Pooled risk periods	53	54.6	6	1917
Pandemrix - Pooled control periods	73	75.3	67	20218
Day0 to Day30 after transplantation	15	15.5	6	425
Day31 to Day90 after transplantation	16	16.5	5	744
Day91 to Day180 after transplantation	14	14.4	2	1110
> 180 days after transplantation	66	68.0	60	19856
Day0 to Day30 after Seasonal vaccine	58	59.8	5	1997
> 30 days after Seasonal vaccine	73	75.3	68	20138

Table 47 Relative incidence of kidney transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and seasonal vaccination (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	30 days after any dose vs. other periods	0.93	0.41	2.08
Time since transplantation	0-30 vs. >180 days	3.77	0.50	28.59
	31-90 vs. >180 days	2.68	0.39	18.38
	91-180 vs. >180 days	0.75	0.08	7.44
Seasonal influenza vaccination	30 days after vaccination vs. other periods	0.61	0.22	1.68

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 48 Kidney transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and respiratory infections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	97	100.0	145	36917
Data after censoring according to transplantations	97	100.0	145	33766
Data after censoring according to second rejection	97	100.0	97	29510
Subjects with at least one exposure of interest (Pandemrix, Respiratory infection, transplantation)	65	67.0	65	19565
Pandemrix - Control period before first dose	65	67.0	24	5478
Pandemrix - Risk period after dose 1	53	54.6	5	1545
Pandemrix - Control period after dose 1	41	42.3	26	9049
Pandemrix - Risk period after dose 2	12	12.4	1	372
Pandemrix - Control period after dose 2	12	12.4	9	3121
Pandemrix - Pooled risk periods	53	54.6	6	1917
Pandemrix - Pooled control periods	65	67.0	59	17648
Day0 to Day30 after transplantation	15	15.5	6	425
Day31 to Day90 after transplantation	16	16.5	5	744
Day91 to Day180 after transplantation	14	14.4	2	1110
> 180 days after transplantation	58	59.8	52	17286
Day0 to Day30 after Respiratory infection	1	1.0	0	31
> 30 days after Respiratory infection	65	67.0	65	19534

Table 49 Relative incidence of kidney transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and respiratory infections (Subset 1a)

No records exist in this table

Table 50 Kidney transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and opportunistic infections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	97	100.0	145	36917
Data after censoring according to transplantations	97	100.0	145	33766
Data after censoring according to second rejection	97	100.0	97	29510
Subjects with at least one exposure of interest (Opportunistic infection, Pandemrix, transplantation)	65	67.0	65	19565
Pandemrix - Control period before first dose	65	67.0	24	5478
Pandemrix - Risk period after dose 1	53	54.6	5	1545
Pandemrix - Control period after dose 1	41	42.3	26	9049
Pandemrix - Risk period after dose 2	12	12.4	1	372
Pandemrix - Control period after dose 2	12	12.4	9	3121
Pandemrix - Pooled risk periods	53	54.6	6	1917
Pandemrix - Pooled control periods	65	67.0	59	17648
Day0 to Day30 after transplantation	15	15.5	6	425
Day31 to Day90 after transplantation	16	16.5	5	744
Day91 to Day180 after transplantation	14	14.4	2	1110
> 180 days after transplantation	58	59.8	52	17286
Day0 to Day30 after Opportunistic infection	4	4.1	1	165
> 30 days after Opportunistic infection	65	67.0	64	19400

Table 51 Relative incidence of kidney transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and opportunistic infections (Subset 1a)

No records exist in this table

Table 52 Kidney transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and acute bacterial infections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	97	100.0	145	36917
Data after censoring according to transplantations	97	100.0	145	33766
Data after censoring according to second rejection	97	100.0	97	29510
Subjects with at least one exposure of interest (Acute bacterial infection, Pandemrix, transplantation)	65	67.0	65	19565
Pandemrix - Control period before first dose	65	67.0	24	5478
Pandemrix - Risk period after dose 1	53	54.6	5	1545
Pandemrix - Control period after dose 1	41	42.3	26	9049
Pandemrix - Risk period after dose 2	12	12.4	1	372
Pandemrix - Control period after dose 2	12	12.4	9	3121
Pandemrix - Pooled risk periods	53	54.6	6	1917
Pandemrix - Pooled control periods	65	67.0	59	17648
Day0 to Day30 after transplantation	15	15.5	6	425
Day31 to Day90 after transplantation	16	16.5	5	744
Day91 to Day180 after transplantation	14	14.4	2	1110
> 180 days after transplantation	58	59.8	52	17286
> 30 days after Acute bacterial infection	65	67.0	65	19565

Table 53 Relative incidence of kidney transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and acute bacterial infections (Subset 1a)

No records exist in this table

Table 54 Kidney transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and chronic viral infections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	94	100.0	142	35729
Data after censoring according to transplantations	94	100.0	142	32578
Data after censoring according to second rejection	94	100.0	94	28322
Subjects with at least one exposure of interest (Chronic viral infection, Pandemrix, transplantation)	63	67.0	63	18773
Pandemrix - Control period before first dose	63	67.0	23	5035
Pandemrix - Risk period after dose 1	52	55.3	5	1514
Pandemrix - Control period after dose 1	40	42.6	25	8731
Pandemrix - Risk period after dose 2	12	12.8	1	372
Pandemrix - Control period after dose 2	12	12.8	9	3121
Pandemrix - Pooled risk periods	52	55.3	6	1886
Pandemrix - Pooled control periods	63	67.0	57	16887
Day0 to Day30 after transplantation	14	14.9	6	419
Day31 to Day90 after transplantation	15	16.0	4	684
Day91 to Day180 after transplantation	13	13.8	2	1020
> 180 days after transplantation	56	59.6	51	16650
> 365 days after Chronic viral infection	63	67.0	63	18773

Table 55 Relative incidence of kidney transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and chronic viral infection (Subset 1a)

No records exist in this table

Table 56 Kidney transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and malignancies/cancers (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	94	100.0	142	35729
Data after censoring according to transplantations	94	100.0	142	32578
Data after censoring according to second rejection	94	100.0	94	28322
Subjects with at least one exposure of interest (Cancer, Pandemrix, transplantation)	64	68.1	64	19169
Pandemrix - Control period before first dose	64	68.1	24	5431
Pandemrix - Risk period after dose 1	52	55.3	5	1514
Pandemrix - Control period after dose 1	40	42.6	25	8731
Pandemrix - Risk period after dose 2	12	12.8	1	372
Pandemrix - Control period after dose 2	12	12.8	9	3121
Pandemrix - Pooled risk periods	52	55.3	6	1886
Pandemrix - Pooled control periods	64	68.1	58	17283
Day0 to Day30 after transplantation	14	14.9	6	419
Day31 to Day90 after transplantation	15	16.0	4	684
Day91 to Day180 after transplantation	13	13.8	2	1020
> 180 days after transplantation	57	60.6	52	17046
Day0 to Day365 after Cancer	6	6.4	4	1444
> 365 days after Cancer	64	68.1	60	17725

Table 57 Relative incidence of kidney transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and malignancies/cancers (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	30 days after any dose vs. other periods	0.89	0.39	2.01
Time since transplantation	0-30 vs. >180 days	2.94	0.40	21.37
	31-90 vs. >180 days	1.89	0.28	12.77
	91-180 vs. >180 days	0.63	0.06	6.45
Malignancies/ cancers	365 days after any record vs. other periods	1.60	0.42	6.01

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 58 Kidney transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and all covariates (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	94	100.0	142	35729
Data after censoring according to transplantations	94	100.0	142	32578
Data after censoring according to second rejection	94	100.0	94	28322
Subjects with at least one exposure of interest (Acute bacterial infection, Cancer, Chronic viral infection, Opportunistic infection, Pandemrix, Respiratory infection, Seasonal vaccine, transplantation)	71	75.5	71	21343
Pandemrix - Control period before first dose	71	75.5	31	7605
Pandemrix - Risk period after dose 1	52	55.3	5	1514
Pandemrix - Control period after dose 1	40	42.6	25	8731
Pandemrix - Risk period after dose 2	12	12.8	1	372
Pandemrix - Control period after dose 2	12	12.8	9	3121
Pandemrix - Pooled risk periods	52	55.3	6	1886
Pandemrix - Pooled control periods	71	75.5	65	19457
Day0 to Day30 after transplantation	14	14.9	6	419
Day31 to Day90 after transplantation	15	16.0	4	684
Day91 to Day180 after transplantation	13	13.8	2	1020
> 180 days after transplantation	64	68.1	59	19220
Day0 to Day30 after Seasonal vaccine	56	59.6	4	1912
> 30 days after Seasonal vaccine	71	75.5	67	19431
Day0 to Day30 after Respiratory infection	1	1.1	0	31
> 30 days after Respiratory infection	71	75.5	71	21312
Day0 to Day30 after Opportunistic infection	4	4.3	1	165
> 30 days after Opportunistic infection	71	75.5	70	21178
> 30 days after Acute bacterial infection	71	75.5	71	21343
> 365 days after Chronic viral infection	71	75.5	71	21343
Day0 to Day365 after Cancer	6	6.4	4	1444
> 365 days after Cancer	71	75.5	67	19899

Table 59 Relative incidence of kidney transplant rejection within 30 days after Pandemrix vaccination adjusted for all covariates (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	30 days after any dose vs. other periods	1.00	0.44	2.25
Time since transplantation	0-30 vs. >180 days	2.94	0.38	22.62
	31-90 vs. >180 days	1.84	0.25	13.22
	91-180 vs. >180 days	0.64	0.06	7.10
Seasonal influenza vaccination	30 days after vaccination vs. other periods	0.51	0.17	1.52
Malignancies/ cancers	365 days after any record vs. other periods	1.49	0.41	5.48

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 60 Kidney transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix and the time since transplantation – with subsequent rejections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	97	100.0	145	36917
Data after censoring according to transplantations	97	100.0	145	33766
Subjects with at least one exposure of interest (Pandemrix, transplantation)	65	67.0	96	22490
Pandemrix - Control period before first dose	65	67.0	26	5562
Pandemrix - Risk period after any dose	53	54.6	8	1976
Pandemrix - Control period after any dose	53	54.6	62	14952
Pandemrix - Pooled risk periods	53	54.6	8	1976
Pandemrix - Pooled control periods	65	67.0	88	20514
Day0 to Day30 after transplantation	15	15.5	6	425
Day31 to Day90 after transplantation	16	16.5	6	768
Day91 to Day180 after transplantation	14	14.4	2	1110
> 180 days after transplantation	58	59.8	82	20187

Table 61 Relative incidence of kidney transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation - not accounting for perturbed post-event exposure (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	30 days after any dose vs. other periods	1.00	0.47	2.09
Time since transplantation	0-30 vs. >180 days	2.24	0.45	11.05
	31-90 vs. >180 days	1.69	0.40	7.20
	91-180 vs. >180 days	0.51	0.09	2.83

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit

Table 62 Relative incidence of kidney transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and conditioned to previous rejections (Subset 1a)

No records exist in this table

Table 63 Kidney transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix and the time since transplantation - Subjects without previous rejections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	58	100.0	81	22308
Data after censoring according to transplantations	58	100.0	81	19787
Data after censoring according to second rejection	58	100.0	58	17907
Subjects with at least one exposure of interest (Pandemrix, transplantation)	58	100.0	58	17907
Pandemrix - Control period before first dose	58	100.0	21	5030
Pandemrix - Risk period after dose 1	46	79.3	4	1328
Pandemrix - Control period after dose 1	35	60.3	23	8056
Pandemrix - Risk period after dose 2	12	20.7	1	372
Pandemrix - Control period after dose 2	12	20.7	9	3121
Pandemrix - Pooled risk periods	46	79.3	5	1700
Pandemrix - Pooled control periods	58	100.0	53	16207
Day0 to Day30 after transplantation	14	24.1	6	409
Day31 to Day90 after transplantation	15	25.9	5	684
Day91 to Day180 after transplantation	12	20.7	1	937
> 180 days after transplantation	51	87.9	46	15877

Table 64 Relative incidence of kidney transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation - Subjects without previous rejections (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	30 days after any dose vs. other periods	0.71	0.30	1.64
Time since transplantation	0-30 vs. >180 days	2.47	0.34	17.65
	31-90 vs. >180 days	1.84	0.27	12.38
	91-180 vs. >180 days	0.17	0.01	2.43

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 65 Kidney transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and previous rejection - Subjects with previous rejections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	7	100.0	15	2703
Data after censoring according to transplantations	7	100.0	15	2703
Data after censoring according to second rejection	7	100.0	7	1658
Subjects with at least one exposure of interest (Pandemrix, Previous rejection, transplantation)	7	100.0	7	1658
Pandemrix - Control period before first dose	7	100.0	3	448
Pandemrix - Risk period after dose 1	7	100.0	1	217
Pandemrix - Control period after dose 1	6	85.7	3	993
Pandemrix - Pooled risk periods	7	100.0	1	217
Pandemrix - Pooled control periods	7	100.0	6	1441
Day0 to Day30 after transplantation	1	14.3	0	16
Day31 to Day90 after transplantation	1	14.3	0	60
Day91 to Day180 after transplantation	2	28.6	1	173
> 180 days after transplantation	7	100.0	6	1409
Day0 to Day180 after Previous rejection	7	100.0	5	750
> 180 days after Previous rejection	4	57.1	2	908

Table 66 Relative incidence of kidney transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and previous rejection - Subjects with previous rejections (Subset 1a)

No records exist in this table

Table 67 Liver transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix and the time since transplantation (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	19	100.0	25	7524
Data after censoring according to transplantations	19	100.0	24	6190
Data after censoring according to second rejection	19	100.0	19	5827
Subjects with at least one exposure of interest (Pandemrix, transplantation)	12	63.2	12	3637
Pandemrix - Control period before first dose	12	63.2	8	1844
Pandemrix - Risk period after dose 1	6	31.6	2	178
Pandemrix - Control period after dose 1	5	26.3	2	1342
Pandemrix - Risk period after dose 2	1	5.3	0	31
Pandemrix - Control period after dose 2	1	5.3	0	242
Pandemrix - Pooled risk periods	6	31.6	2	209
Pandemrix - Pooled control periods	12	63.2	10	3428
Day0 to Day30 after transplantation	6	31.6	4	174
Day31 to Day90 after transplantation	6	31.6	1	300
Day91 to Day180 after transplantation	6	31.6	0	487
> 180 days after transplantation	10	52.6	7	2676

Table 68 Relative incidence of liver transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation (Subset 1a)

No records exist in this table

Table 69 Liver transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and seasonal vaccination (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	19	100.0	25	7524
Data after censoring according to transplantations	19	100.0	24	6190
Data after censoring according to second rejection	19	100.0	19	5827
Subjects with at least one exposure of interest (Pandemrix, Seasonal vaccine, transplantation)	13	68.4	13	3701
Pandemrix - Control period before first dose	13	68.4	9	1908
Pandemrix - Risk period after dose 1	6	31.6	2	178
Pandemrix - Control period after dose 1	5	26.3	2	1342
Pandemrix - Risk period after dose 2	1	5.3	0	31
Pandemrix - Control period after dose 2	1	5.3	0	242
Pandemrix - Pooled risk periods	6	31.6	2	209
Pandemrix - Pooled control periods	13	68.4	11	3492
Day0 to Day30 after transplantation	6	31.6	4	174
Day31 to Day90 after transplantation	6	31.6	1	300
Day91 to Day180 after transplantation	6	31.6	0	487
> 180 days after transplantation	11	57.9	8	2740
Day0 to Day30 after Seasonal vaccine	6	31.6	0	220
> 30 days after Seasonal vaccine	13	68.4	13	3481

Table 70 Relative incidence of liver transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and seasonal vaccination (Subset 1a)

No records exist in this table

Table 71 Liver transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and respiratory infections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	19	100.0	25	7524
Data after censoring according to transplantations	19	100.0	24	6190
Data after censoring according to second rejection	19	100.0	19	5827
Subjects with at least one exposure of interest (Pandemrix, Respiratory infection, transplantation)	12	63.2	12	3637
Pandemrix - Control period before first dose	12	63.2	8	1844
Pandemrix - Risk period after dose 1	6	31.6	2	178
Pandemrix - Control period after dose 1	5	26.3	2	1342
Pandemrix - Risk period after dose 2	1	5.3	0	31
Pandemrix - Control period after dose 2	1	5.3	0	242
Pandemrix - Pooled risk periods	6	31.6	2	209
Pandemrix - Pooled control periods	12	63.2	10	3428
Day0 to Day30 after transplantation	6	31.6	4	174
Day31 to Day90 after transplantation	6	31.6	1	300
Day91 to Day180 after transplantation	6	31.6	0	487
> 180 days after transplantation	10	52.6	7	2676
> 30 days after Respiratory infection	12	63.2	12	3637

Table 72 Relative incidence of liver transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and respiratory infections (Subset 1a)

No records exist in this table

Table 73 Liver transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and opportunistic infections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	19	100.0	25	7524
Data after censoring according to transplantations	19	100.0	24	6190
Data after censoring according to second rejection	19	100.0	19	5827
Subjects with at least one exposure of interest (Opportunistic infection, Pandemrix, transplantation)	12	63.2	12	3637
Pandemrix - Control period before first dose	12	63.2	8	1844
Pandemrix - Risk period after dose 1	6	31.6	2	178
Pandemrix - Control period after dose 1	5	26.3	2	1342
Pandemrix - Risk period after dose 2	1	5.3	0	31
Pandemrix - Control period after dose 2	1	5.3	0	242
Pandemrix - Pooled risk periods	6	31.6	2	209
Pandemrix - Pooled control periods	12	63.2	10	3428
Day0 to Day30 after transplantation	6	31.6	4	174
Day31 to Day90 after transplantation	6	31.6	1	300
Day91 to Day180 after transplantation	6	31.6	0	487
> 180 days after transplantation	10	52.6	7	2676
> 30 days after Opportunistic infection	12	63.2	12	3637

Table 74 Relative incidence of liver transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and opportunistic infections (Subset 1a)

No records exist in this table

Table 75 Liver transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and acute bacterial infections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	19	100.0	25	7524
Data after censoring according to transplantations	19	100.0	24	6190
Data after censoring according to second rejection	19	100.0	19	5827
Subjects with at least one exposure of interest (Acute bacterial infection, Pandemrix, transplantation)	12	63.2	12	3637
Pandemrix - Control period before first dose	12	63.2	8	1844
Pandemrix - Risk period after dose 1	6	31.6	2	178
Pandemrix - Control period after dose 1	5	26.3	2	1342
Pandemrix - Risk period after dose 2	1	5.3	0	31
Pandemrix - Control period after dose 2	1	5.3	0	242
Pandemrix - Pooled risk periods	6	31.6	2	209
Pandemrix - Pooled control periods	12	63.2	10	3428
Day0 to Day30 after transplantation	6	31.6	4	174
Day31 to Day90 after transplantation	6	31.6	1	300
Day91 to Day180 after transplantation	6	31.6	0	487
> 180 days after transplantation	10	52.6	7	2676
> 30 days after Acute bacterial infection	12	63.2	12	3637

Table 76 Relative incidence of liver transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and acute bacterial infections (Subset 1a)

No records exist in this table

Table 77 Liver transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and chronic viral infections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	18	100.0	24	7128
Data after censoring according to transplantations	18	100.0	23	5870
Data after censoring according to second rejection	18	100.0	18	5507
Subjects with at least one exposure of interest (Chronic viral infection, Pandemrix, transplantation)	11	61.1	11	3317
Pandemrix - Control period before first dose	11	61.1	7	1524
Pandemrix - Risk period after dose 1	6	33.3	2	178
Pandemrix - Control period after dose 1	5	27.8	2	1342
Pandemrix - Risk period after dose 2	1	5.6	0	31
Pandemrix - Control period after dose 2	1	5.6	0	242
Pandemrix - Pooled risk periods	6	33.3	2	209
Pandemrix - Pooled control periods	11	61.1	9	3108
Day0 to Day30 after transplantation	5	27.8	3	143
Day31 to Day90 after transplantation	5	27.8	1	240
Day91 to Day180 after transplantation	5	27.8	0	397
> 180 days after transplantation	9	50.0	7	2537
> 365 days after Chronic viral infection	11	61.1	11	3317

Table 78 Relative incidence of liver transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and chronic viral infection (Subset 1a)

No records exist in this table

Table 79 Liver transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and malignancies/cancers (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	18	100.0	24	7128
Data after censoring according to transplantations	18	100.0	23	5870
Data after censoring according to second rejection	18	100.0	18	5507
Subjects with at least one exposure of interest (Cancer, Pandemrix, transplantation)	12	66.7	12	3713
Pandemrix - Control period before first dose	12	66.7	8	1920
Pandemrix - Risk period after dose 1	6	33.3	2	178
Pandemrix - Control period after dose 1	5	27.8	2	1342
Pandemrix - Risk period after dose 2	1	5.6	0	31
Pandemrix - Control period after dose 2	1	5.6	0	242
Pandemrix - Pooled risk periods	6	33.3	2	209
Pandemrix - Pooled control periods	12	66.7	10	3504
Day0 to Day30 after transplantation	5	27.8	3	143
Day31 to Day90 after transplantation	5	27.8	1	240
Day91 to Day180 after transplantation	5	27.8	0	397
> 180 days after transplantation	10	55.6	8	2933
Day0 to Day365 after Cancer	3	16.7	2	541
> 365 days after Cancer	12	66.7	10	3172

Table 80 Relative incidence of liver transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and malignancies/cancers (Subset 1a)

No records exist in this table

Table 81 Liver transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and all covariates (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	18	100.0	24	7128
Data after censoring according to transplantations	18	100.0	23	5870
Data after censoring according to second rejection	18	100.0	18	5507
Subjects with at least one exposure of interest (Acute bacterial infection, Cancer, Chronic viral infection, Opportunistic infection, Pandemrix, Respiratory infection, Seasonal vaccine, transplantation)	13	72.2	13	3777
Pandemrix - Control period before first dose	13	72.2	9	1984
Pandemrix - Risk period after dose 1	6	33.3	2	178
Pandemrix - Control period after dose 1	5	27.8	2	1342
Pandemrix - Risk period after dose 2	1	5.6	0	31
Pandemrix - Control period after dose 2	1	5.6	0	242
Pandemrix - Pooled risk periods	6	33.3	2	209
Pandemrix - Pooled control periods	13	72.2	11	3568
Day0 to Day30 after transplantation	5	27.8	3	143
Day31 to Day90 after transplantation	5	27.8	1	240
Day91 to Day180 after transplantation	5	27.8	0	397
> 180 days after transplantation	11	61.1	9	2997
Day0 to Day30 after Seasonal vaccine	6	33.3	0	220
> 30 days after Seasonal vaccine	13	72.2	13	3557
> 30 days after Respiratory infection	13	72.2	13	3777
> 30 days after Opportunistic infection	13	72.2	13	3777
> 30 days after Acute bacterial infection	13	72.2	13	3777
> 365 days after Chronic viral infection	13	72.2	13	3777
Day0 to Day365 after Cancer	3	16.7	2	541
> 365 days after Cancer	13	72.2	11	3236

Table 82 Relative incidence of liver transplant rejection within 30 days after Pandemrix vaccination adjusted for all covariates (Subset 1a)

No records exist in this table

Table 83 Liver transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix and the time since transplantation – with subsequent rejections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	19	100.0	25	7524
Data after censoring according to transplantations	19	100.0	24	6190
Subjects with at least one exposure of interest (Pandemrix, transplantation)	12	63.2	16	3928
Pandemrix - Control period before first dose	12	63.2	12	2135
Pandemrix - Risk period after any dose	6	31.6	2	209
Pandemrix - Control period after any dose	6	31.6	2	1584
Pandemrix - Pooled risk periods	6	31.6	2	209
Pandemrix - Pooled control periods	12	63.2	14	3719
Day0 to Day30 after transplantation	6	31.6	4	174
Day31 to Day90 after transplantation	6	31.6	3	360
Day91 to Day180 after transplantation	8	42.1	0	595
> 180 days after transplantation	11	57.9	9	2799

Table 84 Relative incidence of liver transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation - not accounting for perturbed post-event exposure (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	30 days after any dose vs. other periods	4.35	0.77	24.46
Time since transplantation	0-30 vs. >180 days	3.81	0.76	19.06
	31-90 vs. >180 days	1.43	0.26	7.80
	91-180 vs. >180 days	0.00	0.00	.

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit

Table 85 Relative incidence of liver transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and conditioned to previous rejections (Subset 1a)

No records exist in this table

Table 86 Liver transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix and the time since transplantation - Subjects without previous rejections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	11	100.0	15	4356
Data after censoring according to transplantations	11	100.0	15	3668
Data after censoring according to second rejection	11	100.0	11	3377
Subjects with at least one exposure of interest (Pandemrix, transplantation)	11	100.0	11	3377
Pandemrix - Control period before first dose	11	100.0	8	1745
Pandemrix - Risk period after dose 1	5	45.5	2	147
Pandemrix - Control period after dose 1	4	36.4	1	1212
Pandemrix - Risk period after dose 2	1	9.1	0	31
Pandemrix - Control period after dose 2	1	9.1	0	242
Pandemrix - Pooled risk periods	5	45.5	2	178
Pandemrix - Pooled control periods	11	100.0	9	3199
Day0 to Day30 after transplantation	6	54.5	4	174
Day31 to Day90 after transplantation	6	54.5	1	300
Day91 to Day180 after transplantation	5	45.5	0	398
> 180 days after transplantation	9	81.8	6	2505

Table 87 Relative incidence of liver transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation - Subjects without previous rejections (Subset 1a)

No records exist in this table

Table 88 Liver transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and previous rejection - Subjects with previous rejections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	1	100.0	1	396
Data after censoring according to transplantations	1	100.0	1	260
Data after censoring according to second rejection	1	100.0	1	260
Subjects with at least one exposure of interest (Pandemrix, Previous rejection, transplantation)	1	100.0	1	260
Pandemrix - Control period before first dose	1	100.0	0	99
Pandemrix - Risk period after dose 1	1	100.0	0	31
Pandemrix - Control period after dose 1	1	100.0	1	130
Pandemrix - Pooled risk periods	1	100.0	0	31
Pandemrix - Pooled control periods	1	100.0	1	229
Day91 to Day180 after transplantation	1	100.0	0	89
> 180 days after transplantation	1	100.0	1	171
Day0 to Day180 after Previous rejection	1	100.0	0	83
> 180 days after Previous rejection	1	100.0	1	177

Table 89 Relative incidence of liver transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and previous rejection - Subjects with previous rejections (Subset 1a)

No records exist in this table

Table 90 Lung transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix and the time since transplantation (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	5	100.0	6	1904
Data after censoring according to transplantations	5	100.0	6	1670
Data after censoring according to second rejection	5	100.0	5	1558
Subjects with at least one exposure of interest (Pandemrix, transplantation)	4	80.0	4	1238
Pandemrix - Control period before first dose	4	80.0	2	345
Pandemrix - Risk period after dose 1	3	60.0	0	72
Pandemrix - Control period after dose 1	1	20.0	0	290
Pandemrix - Risk period after dose 2	2	40.0	0	62
Pandemrix - Control period after dose 2	2	40.0	2	469
Pandemrix - Pooled risk periods	3	60.0	0	134
Pandemrix - Pooled control periods	4	80.0	4	1104
Day0 to Day30 after transplantation	2	40.0	0	41
Day31 to Day90 after transplantation	2	40.0	1	120
Day91 to Day180 after transplantation	2	40.0	0	161
> 180 days after transplantation	3	60.0	3	916

Table 91 Pancreas transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix and the time since transplantation (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	1	100.0	1	208
Data after censoring according to transplantations	1	100.0	1	208
Data after censoring according to second rejection	1	100.0	1	208
Subjects with at least one exposure of interest (Pandemrix, transplantation)	1	100.0	1	208
Pandemrix - Control period before first dose	1	100.0	1	57
Pandemrix - Risk period after dose 1	1	100.0	0	31
Pandemrix - Control period after dose 1	1	100.0	0	120
Pandemrix - Pooled risk periods	1	100.0	0	31
Pandemrix - Pooled control periods	1	100.0	1	177
Day91 to Day180 after transplantation	1	100.0	0	15
> 180 days after transplantation	1	100.0	1	193

Table 92 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix and the time since transplantation (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	67	100.0	95	25687
Data after censoring according to transplantations	67	100.0	95	22452
Data after censoring according to second rejection	67	100.0	67	20095
Subjects with at least one exposure of interest (Pandemrix, transplantation)	39	58.2	39	10661
Pandemrix - Control period before first dose	39	58.2	18	3937
Pandemrix - Risk period after dose 1	26	38.8	2	740
Pandemrix - Control period after dose 1	19	28.4	13	4009
Pandemrix - Risk period after dose 2	8	11.9	1	248
Pandemrix - Control period after dose 2	8	11.9	5	1727
Pandemrix - Pooled risk periods	26	38.8	3	988
Pandemrix - Pooled control periods	39	58.2	36	9673
Day0 to Day30 after transplantation	16	23.9	6	460
Day31 to Day90 after transplantation	16	23.9	5	779
Day91 to Day180 after transplantation	16	23.9	2	1236
> 180 days after transplantation	32	47.8	26	8186

Figure 12 Frequency of rejections per day after transplantation (Subset 1b)

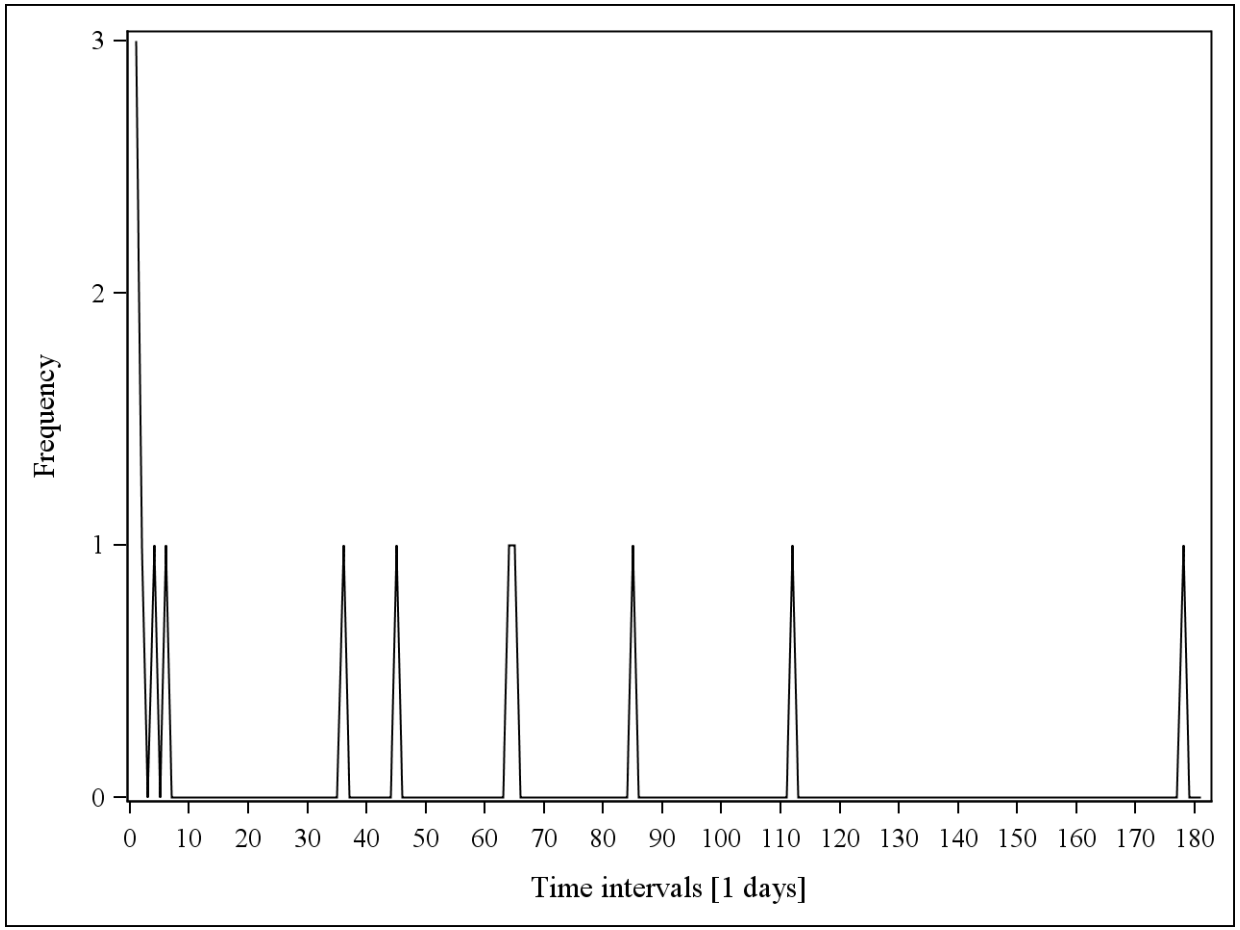

Figure 13 Frequency of rejections per week after transplantation (Subset 1b)

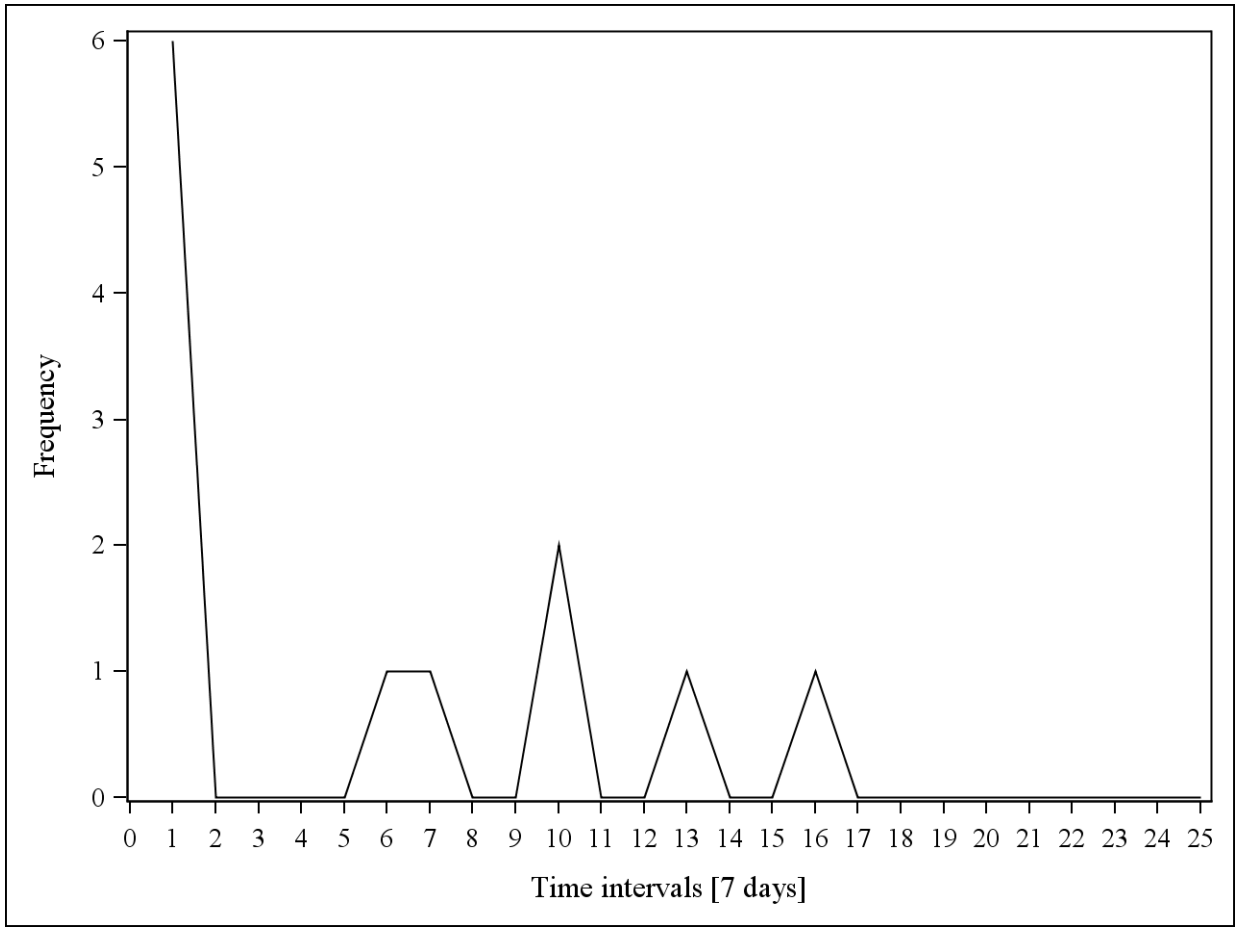

Figure 14 Frequency of rejections per month after transplantation (Subset 1b)

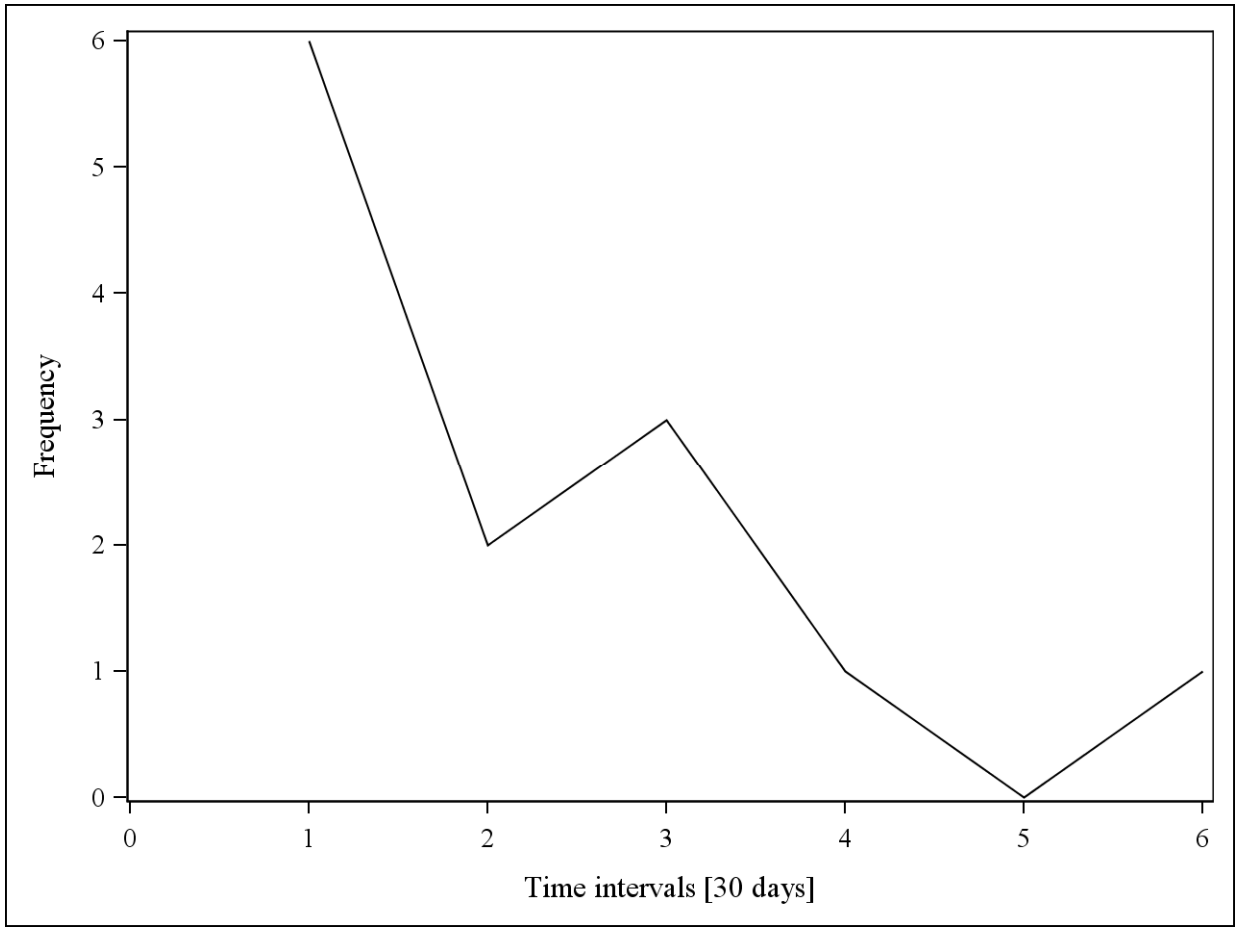

Figure 15 Frequency of rejections by week (Subset 1b)

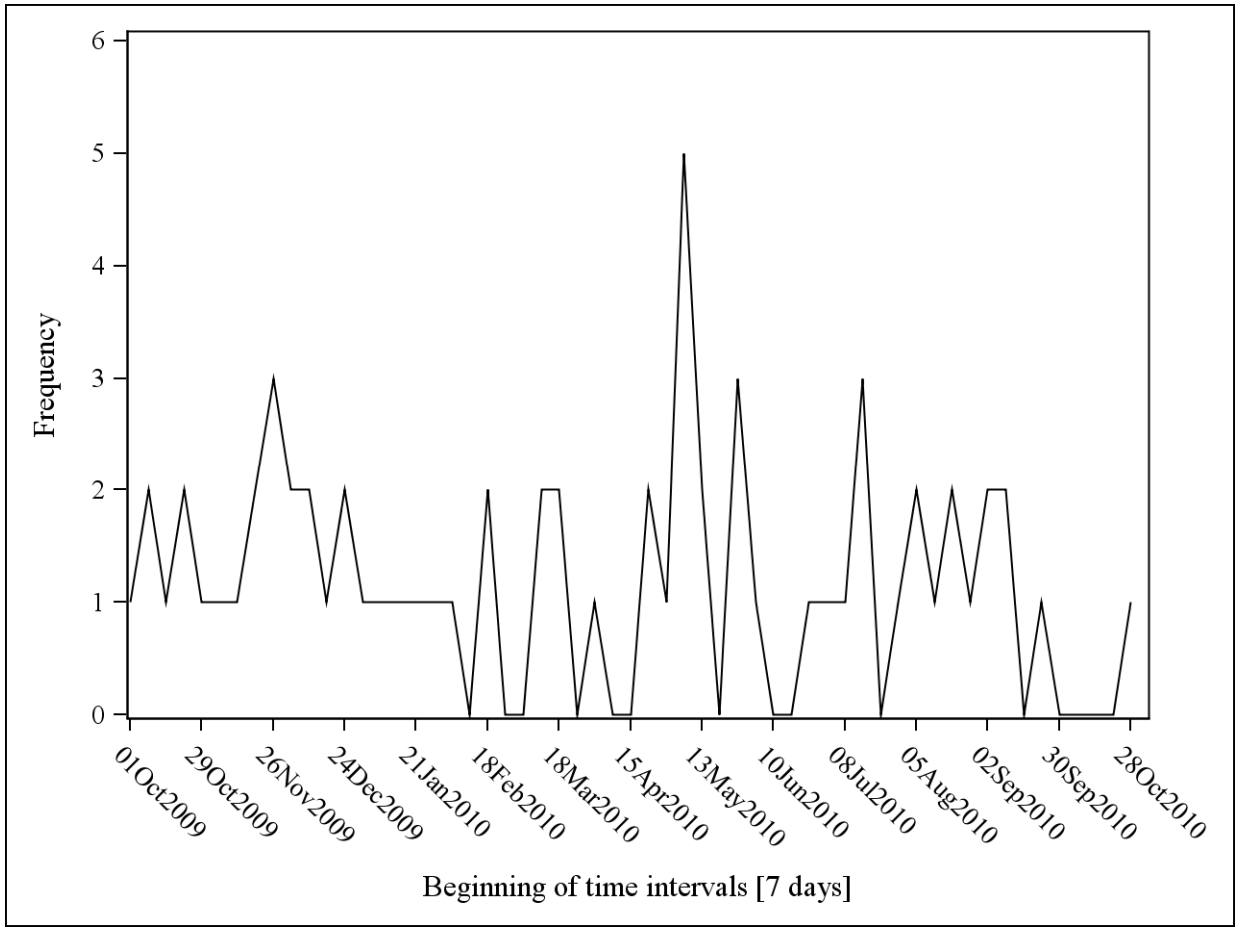

Figure 16 Frequency of rejections by month (Subset 1b)

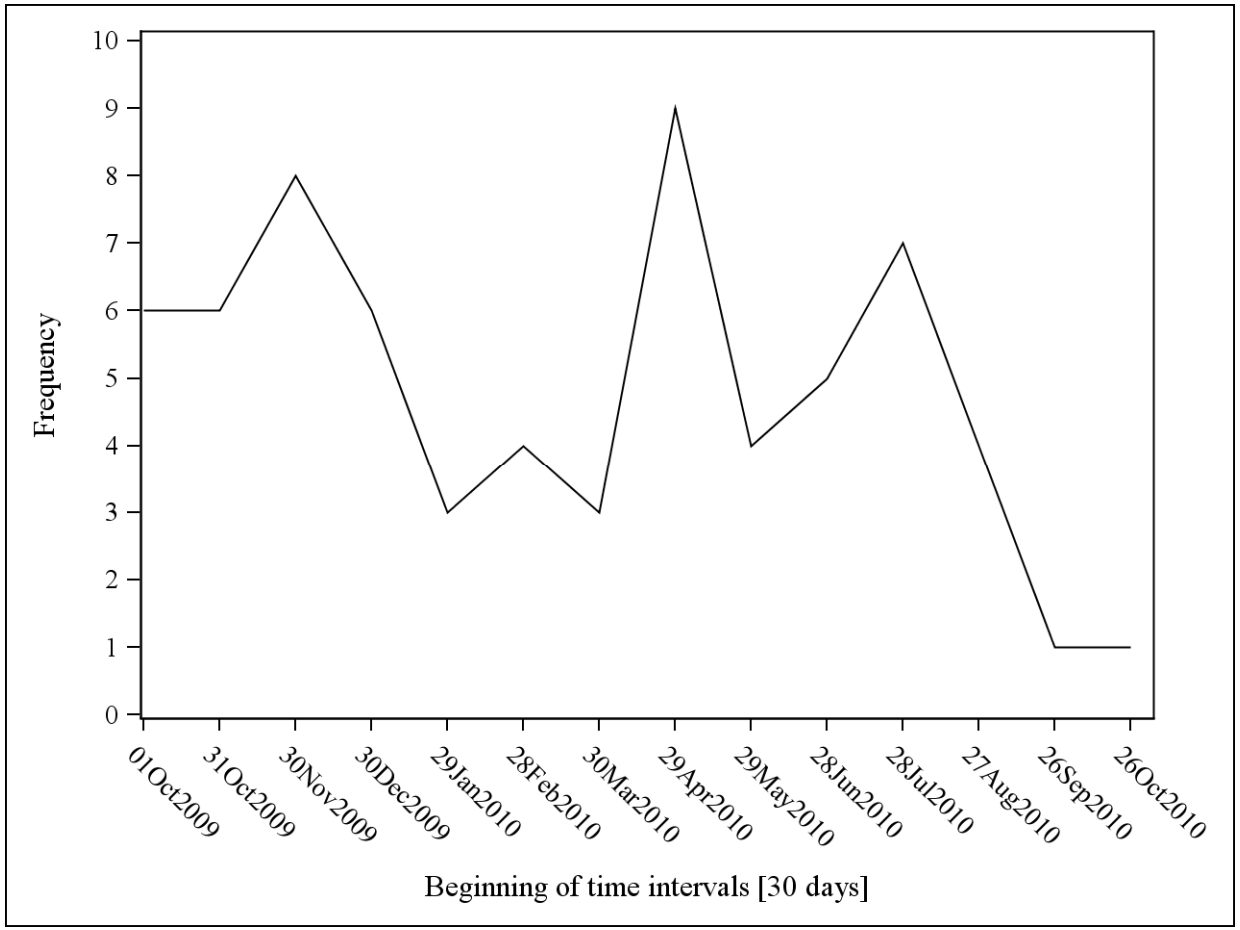

Table 93 Relative incidence of SOT rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation (Subset 1b)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	30 days after any dose vs. other periods	0.70	0.23	2.11
Time since transplantation	0-30 vs. >180 days	2.09	0.36	12.04
	31-90 vs. >180 days	1.61	0.38	6.72
	91-180 vs. >180 days	0.42	0.05	3.45

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 94 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and seasonal vaccination (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	67	100.0	95	25687
Data after censoring according to transplantations	67	100.0	95	22452
Data after censoring according to second rejection	67	100.0	67	20095
Subjects with at least one exposure of interest (Pandemrix, Seasonal vaccine, transplantation)	49	73.1	49	13868
Pandemrix - Control period before first dose	49	73.1	28	7144
Pandemrix - Risk period after dose 1	26	38.8	2	740
Pandemrix - Control period after dose 1	19	28.4	13	4009
Pandemrix - Risk period after dose 2	8	11.9	1	248
Pandemrix - Control period after dose 2	8	11.9	5	1727
Pandemrix - Pooled risk periods	26	38.8	3	988
Pandemrix - Pooled control periods	49	73.1	46	12880
Day0 to Day30 after transplantation	16	23.9	6	460
Day31 to Day90 after transplantation	16	23.9	5	779
Day91 to Day180 after transplantation	16	23.9	2	1236
> 180 days after transplantation	42	62.7	36	11393
Day0 to Day30 after Seasonal vaccine	30	44.8	1	1003
> 30 days after Seasonal vaccine	49	73.1	48	12865

Table 95 Relative incidence of SOT rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and seasonal vaccination (Subset 1b)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	30 days after any dose vs. other periods	0.75	0.26	2.22
Time since transplantation	0-30 vs. >180 days	2.12	0.36	12.65
	31-90 vs. >180 days	1.59	0.36	6.97
	91-180 vs. >180 days	0.43	0.05	3.83
Seasonal influenza vaccination	30 days after vaccination vs. other periods	0.51	0.09	3.03

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 96 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and respiratory infections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	67	100.0	95	25687
Data after censoring according to transplantations	67	100.0	95	22452
Data after censoring according to second rejection	67	100.0	67	20095
Subjects with at least one exposure of interest (Pandemrix, Respiratory infection, transplantation)	40	59.7	40	10995
Pandemrix - Control period before first dose	40	59.7	19	4271
Pandemrix - Risk period after dose 1	26	38.8	2	740
Pandemrix - Control period after dose 1	19	28.4	13	4009
Pandemrix - Risk period after dose 2	8	11.9	1	248
Pandemrix - Control period after dose 2	8	11.9	5	1727
Pandemrix - Pooled risk periods	26	38.8	3	988
Pandemrix - Pooled control periods	40	59.7	37	10007
Day0 to Day30 after transplantation	16	23.9	6	460
Day31 to Day90 after transplantation	16	23.9	5	779
Day91 to Day180 after transplantation	16	23.9	2	1236
> 180 days after transplantation	33	49.3	27	8520
Day0 to Day30 after Respiratory infection	3	4.5	0	93
> 30 days after Respiratory infection	40	59.7	40	10902

Table 97 Relative incidence of SOT rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and respiratory infections (Subset 1b)

No records exist in this table

Table 98 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and opportunistic infections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	67	100.0	95	25687
Data after censoring according to transplantations	67	100.0	95	22452
Data after censoring according to second rejection	67	100.0	67	20095
Subjects with at least one exposure of interest (Opportunistic infection, Pandemrix, transplantation)	40	59.7	40	11057
Pandemrix - Control period before first dose	40	59.7	19	4333
Pandemrix - Risk period after dose 1	26	38.8	2	740
Pandemrix - Control period after dose 1	19	28.4	13	4009
Pandemrix - Risk period after dose 2	8	11.9	1	248
Pandemrix - Control period after dose 2	8	11.9	5	1727
Pandemrix - Pooled risk periods	26	38.8	3	988
Pandemrix - Pooled control periods	40	59.7	37	10069
Day0 to Day30 after transplantation	16	23.9	6	460
Day31 to Day90 after transplantation	16	23.9	5	779
Day91 to Day180 after transplantation	16	23.9	2	1236
> 180 days after transplantation	33	49.3	27	8582
Day0 to Day30 after Opportunistic infection	4	6.0	0	175
> 30 days after Opportunistic infection	40	59.7	40	10882

Table 99 Relative incidence of SOT rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and opportunistic infections (Subset 1b)

No records exist in this table

Table 100 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and acute bacterial infections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	67	100.0	95	25687
Data after censoring according to transplantations	67	100.0	95	22452
Data after censoring according to second rejection	67	100.0	67	20095
Subjects with at least one exposure of interest (Acute bacterial infection, Pandemrix, transplantation)	39	58.2	39	10661
Pandemrix - Control period before first dose	39	58.2	18	3937
Pandemrix - Risk period after dose 1	26	38.8	2	740
Pandemrix - Control period after dose 1	19	28.4	13	4009
Pandemrix - Risk period after dose 2	8	11.9	1	248
Pandemrix - Control period after dose 2	8	11.9	5	1727
Pandemrix - Pooled risk periods	26	38.8	3	988
Pandemrix - Pooled control periods	39	58.2	36	9673
Day0 to Day30 after transplantation	16	23.9	6	460
Day31 to Day90 after transplantation	16	23.9	5	779
Day91 to Day180 after transplantation	16	23.9	2	1236
> 180 days after transplantation	32	47.8	26	8186
> 30 days after Acute bacterial infection	39	58.2	39	10661

Table 101 Relative incidence of SOT rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and acute bacterial infections (Subset 1b)

No records exist in this table

Table 102 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and chronic viral infections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	65	100.0	92	24895
Data after censoring according to transplantations	65	100.0	92	21736
Data after censoring according to second rejection	65	100.0	65	19462
Subjects with at least one exposure of interest (Chronic viral infection, Pandemrix, transplantation)	38	58.5	38	10341
Pandemrix - Control period before first dose	38	58.5	17	3617
Pandemrix - Risk period after dose 1	26	40.0	2	740
Pandemrix - Control period after dose 1	19	29.2	13	4009
Pandemrix - Risk period after dose 2	8	12.3	1	248
Pandemrix - Control period after dose 2	8	12.3	5	1727
Pandemrix - Pooled risk periods	26	40.0	3	988
Pandemrix - Pooled control periods	38	58.5	35	9353
Day0 to Day30 after transplantation	15	23.1	5	429
Day31 to Day90 after transplantation	15	23.1	5	719
Day91 to Day180 after transplantation	15	23.1	2	1146
> 180 days after transplantation	31	47.7	26	8047
> 365 days after Chronic viral infection	38	58.5	38	10341

Table 103 Relative incidence of SOT rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and chronic viral infection (Subset 1b)

No records exist in this table

Table 104 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and malignancies/cancers (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	65	100.0	92	24895
Data after censoring according to transplantations	65	100.0	92	21736
Data after censoring according to second rejection	65	100.0	65	19462
Subjects with at least one exposure of interest (Cancer, Pandemrix, transplantation)	39	60.0	39	10737
Pandemrix - Control period before first dose	39	60.0	18	4013
Pandemrix - Risk period after dose 1	26	40.0	2	740
Pandemrix - Control period after dose 1	19	29.2	13	4009
Pandemrix - Risk period after dose 2	8	12.3	1	248
Pandemrix - Control period after dose 2	8	12.3	5	1727
Pandemrix - Pooled risk periods	26	40.0	3	988
Pandemrix - Pooled control periods	39	60.0	36	9749
Day0 to Day30 after transplantation	15	23.1	5	429
Day31 to Day90 after transplantation	15	23.1	5	719
Day91 to Day180 after transplantation	15	23.1	2	1146
> 180 days after transplantation	32	49.2	27	8443
Day0 to Day365 after Cancer	2	3.1	2	402
> 365 days after Cancer	39	60.0	37	10335

Table 105 Relative incidence of SOT rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and malignancies/cancers (Subset 1b)

No records exist in this table

Table 106 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and chemotherapy (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	65	100.0	92	24895
Data after censoring according to transplantations	65	100.0	92	21736
Data after censoring according to second rejection	65	100.0	65	19462
Subjects with at least one exposure of interest (Chemotherapy, Pandemrix, transplantation)	41	63.1	41	11529
Pandemrix - Control period before first dose	41	63.1	20	4805
Pandemrix - Risk period after dose 1	26	40.0	2	740
Pandemrix - Control period after dose 1	19	29.2	13	4009
Pandemrix - Risk period after dose 2	8	12.3	1	248
Pandemrix - Control period after dose 2	8	12.3	5	1727
Pandemrix - Pooled risk periods	26	40.0	3	988
Pandemrix - Pooled control periods	41	63.1	38	10541
Day0 to Day30 after transplantation	15	23.1	5	429
Day31 to Day90 after transplantation	15	23.1	5	719
Day91 to Day180 after transplantation	15	23.1	2	1146
> 180 days after transplantation	34	52.3	29	9235
Day0 to Day365 after Chemotherapy	5	7.7	2	1336
> 365 days after Chemotherapy	40	61.5	39	10193

Table 107 Relative incidence of SOT rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and chemotherapy (Subset 1b)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	30 days after any dose vs. other periods	0.72	0.24	2.16
Time since transplantation	0-30 vs. >180 days	1.07	0.11	10.48
	31-90 vs. >180 days	1.29	0.23	7.31
	91-180 vs. >180 days	0.37	0.03	4.59
Chemotherapy	365 days after treatment vs. other periods	0.07	0.01	0.91

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 108 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and all covariates (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	65	100.0	92	24895
Data after censoring according to transplantations	65	100.0	92	21736
Data after censoring according to second rejection	65	100.0	65	19462
Subjects with at least one exposure of interest (Acute bacterial infection, Cancer, Chemotherapy, Chronic viral infection, Opportunistic infection, Pandemrix, Respiratory infection, Seasonal vaccine, transplantation)	51	78.5	51	14674
Pandemrix - Control period before first dose	51	78.5	30	7950
Pandemrix - Risk period after dose 1	26	40.0	2	740
Pandemrix - Control period after dose 1	19	29.2	13	4009
Pandemrix - Risk period after dose 2	8	12.3	1	248
Pandemrix - Control period after dose 2	8	12.3	5	1727
Pandemrix - Pooled risk periods	26	40.0	3	988
Pandemrix - Pooled control periods	51	78.5	48	13686
Day0 to Day30 after transplantation	15	23.1	5	429
Day31 to Day90 after transplantation	15	23.1	5	719
Day91 to Day180 after transplantation	15	23.1	2	1146
> 180 days after transplantation	44	67.7	39	12380
Day0 to Day30 after Seasonal vaccine	30	46.2	1	1003
> 30 days after Seasonal vaccine	51	78.5	50	13671
Day0 to Day30 after Respiratory infection	3	4.6	0	93
> 30 days after Respiratory infection	51	78.5	51	14581
Day0 to Day30 after Opportunistic infection	4	6.2	0	175
> 30 days after Opportunistic infection	51	78.5	51	14499
> 30 days after Acute bacterial infection	51	78.5	51	14674
> 365 days after Chronic viral infection	51	78.5	51	14674
Day0 to Day365 after Cancer	2	3.1	2	402
> 365 days after Cancer	51	78.5	49	14272
Day0 to Day365 after Chemotherapy	5	7.7	2	1336
> 365 days after Chemotherapy	50	76.9	49	13338

Table 109 Relative incidence of SOT rejection within 30 days after Pandemrix vaccination adjusted for all covariates (Subset 1b)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	30 days after any dose vs. other periods	0.77	0.26	2.27
Time since transplantation	0-30 vs. >180 days	1.07	0.10	11.15
	31-90 vs. >180 days	1.27	0.21	7.73
	91-180 vs. >180 days	0.38	0.03	5.14
Seasonal influenza vaccination	30 days after vaccination vs. other periods	0.51	0.08	3.12
Chemotherapy	365 days after treatment vs. other periods	0.07	0.01	0.94

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 110 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix and the time since transplantation – with subsequent rejections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	67	100.0	95	25687
Data after censoring according to transplantations	67	100.0	95	22452
Subjects with at least one exposure of interest (Pandemrix, transplantation)	39	58.2	55	12084
Pandemrix - Control period before first dose	39	58.2	25	4163
Pandemrix - Risk period after any dose	27	40.3	3	1019
Pandemrix - Control period after any dose	27	40.3	27	6902
Pandemrix - Pooled risk periods	27	40.3	3	1019
Pandemrix - Pooled control periods	39	58.2	52	11065
Day0 to Day30 after transplantation	16	23.9	6	460
Day31 to Day90 after transplantation	16	23.9	7	836
Day91 to Day180 after transplantation	17	25.4	2	1254
> 180 days after transplantation	32	47.8	40	9534

Table 111 Relative incidence of SOT rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation - not accounting for perturbed post-event exposure (Subset 1b)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	30 days after any dose vs. other periods	0.76	0.23	2.55
Time since transplantation	0-30 vs. >180 days	0.89	0.23	3.46
	31-90 vs. >180 days	0.74	0.22	2.46
	91-180 vs. >180 days	0.20	0.04	0.99

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit

Table 112 Relative incidence of SOT rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and conditioned to previous rejections (Subset 1b)

No records exist in this table

Table 113 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix and the time since transplantation - subjects without previous rejections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	33	100.0	46	12680
Data after censoring according to transplantations	33	100.0	46	9913
Data after censoring according to second rejection	33	100.0	33	8908
Subjects with at least one exposure of interest (Pandemrix, transplantation)	33	100.0	33	8908
Pandemrix - Control period before first dose	33	100.0	17	3514
Pandemrix - Risk period after dose 1	20	60.6	1	565
Pandemrix - Control period after dose 1	14	42.4	9	2936
Pandemrix - Risk period after dose 2	7	21.2	1	217
Pandemrix - Control period after dose 2	7	21.2	5	1676
Pandemrix - Pooled risk periods	20	60.6	2	782
Pandemrix - Pooled control periods	33	100.0	31	8126
Day0 to Day30 after transplantation	14	42.4	6	434
Day31 to Day90 after transplantation	14	42.4	4	659
Day91 to Day180 after transplantation	12	36.4	1	884
> 180 days after transplantation	26	78.8	22	6931

Table 114 Relative incidence of SOT rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation - Subjects without previous rejections (Subset 1b)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	30 days after any dose vs. other periods	0.43	0.15	1.25
Time since transplantation	0-30 vs. >180 days	1.24	0.20	7.79
	31-90 vs. >180 days	0.99	0.23	4.19
	91-180 vs. >180 days	0.08	0.01	1.19

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 115 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and previous rejection - Subjects with previous rejections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	6	100.0	9	2307
Data after censoring according to transplantations	6	100.0	9	2171
Data after censoring according to second rejection	6	100.0	6	1753
Subjects with at least one exposure of interest (Pandemrix, Previous rejection, transplantation)	6	100.0	6	1753
Pandemrix - Control period before first dose	6	100.0	1	423
Pandemrix - Risk period after dose 1	6	100.0	1	175
Pandemrix - Control period after dose 1	5	83.3	4	1073
Pandemrix - Risk period after dose 2	1	16.7	0	31
Pandemrix - Control period after dose 2	1	16.7	0	51
Pandemrix - Pooled risk periods	6	100.0	1	206
Pandemrix - Pooled control periods	6	100.0	5	1547
Day0 to Day30 after transplantation	2	33.3	0	26
Day31 to Day90 after transplantation	2	33.3	1	120
Day91 to Day180 after transplantation	4	66.7	1	352
> 180 days after transplantation	6	100.0	4	1255
Day0 to Day180 after Previous rejection	6	100.0	3	664
> 180 days after Previous rejection	5	83.3	3	1089

Table 116 Relative incidence of SOT rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and previous rejection - Subjects with previous rejections (Subset 1b)

No records exist in this table

Table 117 Heart transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix and the time since transplantation (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	3	100.0	4	1188
Data after censoring according to transplantations	3	100.0	4	1038
Data after censoring according to second rejection	3	100.0	3	938
Subjects with at least one exposure of interest (Pandemrix, transplantation)	2	66.7	2	642
Pandemrix - Control period before first dose	2	66.7	0	91
Pandemrix - Risk period after dose 1	2	66.7	0	62
Pandemrix - Control period after dose 1	2	66.7	2	489
Pandemrix - Pooled risk periods	2	66.7	0	62
Pandemrix - Pooled control periods	2	66.7	2	580
> 180 days after transplantation	2	66.7	2	642

Table 118 Kidney transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix and the time since transplantation (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	34	100.0	51	13007
Data after censoring according to transplantations	34	100.0	51	11071
Data after censoring according to second rejection	34	100.0	34	9626
Subjects with at least one exposure of interest (Pandemrix, transplantation)	26	76.5	26	7003
Pandemrix - Control period before first dose	26	76.5	11	2495
Pandemrix - Risk period after dose 1	18	52.9	1	521
Pandemrix - Control period after dose 1	14	41.2	9	2698
Pandemrix - Risk period after dose 2	5	14.7	1	155
Pandemrix - Control period after dose 2	5	14.7	4	1134
Pandemrix - Pooled risk periods	18	52.9	2	676
Pandemrix - Pooled control periods	26	76.5	24	6327
Day0 to Day30 after transplantation	11	32.4	3	326
Day31 to Day90 after transplantation	11	32.4	3	512
Day91 to Day180 after transplantation	10	29.4	2	768
> 180 days after transplantation	21	61.8	18	5397

Table 119 Relative incidence of kidney transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation (Subset 1b)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	30 days after any dose vs. other periods	0.58	0.18	1.89
Time since transplantation	0-30 vs. >180 days	0.85	0.12	6.08
	31-90 vs. >180 days	1.49	0.31	7.17
	91-180 vs. >180 days	0.62	0.06	6.89

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 120 Kidney transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and seasonal vaccination (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	34	100.0	51	13007
Data after censoring according to transplantations	34	100.0	51	11071
Data after censoring according to second rejection	34	100.0	34	9626
Subjects with at least one exposure of interest (Pandemrix, Seasonal vaccine, transplantation)	28	82.4	28	7790
Pandemrix - Control period before first dose	28	82.4	13	3282
Pandemrix - Risk period after dose 1	18	52.9	1	521
Pandemrix - Control period after dose 1	14	41.2	9	2698
Pandemrix - Risk period after dose 2	5	14.7	1	155
Pandemrix - Control period after dose 2	5	14.7	4	1134
Pandemrix - Pooled risk periods	18	52.9	2	676
Pandemrix - Pooled control periods	28	82.4	26	7114
Day0 to Day30 after transplantation	11	32.4	3	326
Day31 to Day90 after transplantation	11	32.4	3	512
Day91 to Day180 after transplantation	10	29.4	2	768
> 180 days after transplantation	23	67.6	20	6184
Day0 to Day30 after Seasonal vaccine	16	47.1	1	552
> 30 days after Seasonal vaccine	28	82.4	27	7238

Table 121 Relative incidence of kidney transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and seasonal vaccination (Subset 1b)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	30 days after any dose vs. other periods	0.56	0.21	1.50
Time since transplantation	0-30 vs. >180 days	0.86	0.11	6.47
	31-90 vs. >180 days	1.51	0.29	7.85
	91-180 vs. >180 days	0.62	0.05	7.93
Seasonal influenza vaccination	30 days after vaccination vs. other periods	1.18	0.26	5.34

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 122 Kidney transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and respiratory infections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	34	100.0	51	13007
Data after censoring according to transplantations	34	100.0	51	11071
Data after censoring according to second rejection	34	100.0	34	9626
Subjects with at least one exposure of interest (Pandemrix, Respiratory infection, transplantation)	27	79.4	27	7337
Pandemrix - Control period before first dose	27	79.4	12	2829
Pandemrix - Risk period after dose 1	18	52.9	1	521
Pandemrix - Control period after dose 1	14	41.2	9	2698
Pandemrix - Risk period after dose 2	5	14.7	1	155
Pandemrix - Control period after dose 2	5	14.7	4	1134
Pandemrix - Pooled risk periods	18	52.9	2	676
Pandemrix - Pooled control periods	27	79.4	25	6661
Day0 to Day30 after transplantation	11	32.4	3	326
Day31 to Day90 after transplantation	11	32.4	3	512
Day91 to Day180 after transplantation	10	29.4	2	768
> 180 days after transplantation	22	64.7	19	5731
Day0 to Day30 after Respiratory infection	3	8.8	0	93
> 30 days after Respiratory infection	27	79.4	27	7244

Table 123 Relative incidence of kidney transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and respiratory infections (Subset 1b)

No records exist in this table

Table 124 Kidney transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and opportunistic infections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	34	100.0	51	13007
Data after censoring according to transplantations	34	100.0	51	11071
Data after censoring according to second rejection	34	100.0	34	9626
Subjects with at least one exposure of interest (Opportunistic infection, Pandemrix, transplantation)	26	76.5	26	7003
Pandemrix - Control period before first dose	26	76.5	11	2495
Pandemrix - Risk period after dose 1	18	52.9	1	521
Pandemrix - Control period after dose 1	14	41.2	9	2698
Pandemrix - Risk period after dose 2	5	14.7	1	155
Pandemrix - Control period after dose 2	5	14.7	4	1134
Pandemrix - Pooled risk periods	18	52.9	2	676
Pandemrix - Pooled control periods	26	76.5	24	6327
Day0 to Day30 after transplantation	11	32.4	3	326
Day31 to Day90 after transplantation	11	32.4	3	512
Day91 to Day180 after transplantation	10	29.4	2	768
> 180 days after transplantation	21	61.8	18	5397
Day0 to Day30 after Opportunistic infection	2	5.9	0	80
> 30 days after Opportunistic infection	26	76.5	26	6923

Table 125 Relative incidence of kidney transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and opportunistic infections (Subset 1b)

No records exist in this table

Table 126 Kidney transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and acute bacterial infections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	34	100.0	51	13007
Data after censoring according to transplantations	34	100.0	51	11071
Data after censoring according to second rejection	34	100.0	34	9626
Subjects with at least one exposure of interest (Acute bacterial infection, Pandemrix, transplantation)	26	76.5	26	7003
Pandemrix - Control period before first dose	26	76.5	11	2495
Pandemrix - Risk period after dose 1	18	52.9	1	521
Pandemrix - Control period after dose 1	14	41.2	9	2698
Pandemrix - Risk period after dose 2	5	14.7	1	155
Pandemrix - Control period after dose 2	5	14.7	4	1134
Pandemrix - Pooled risk periods	18	52.9	2	676
Pandemrix - Pooled control periods	26	76.5	24	6327
Day0 to Day30 after transplantation	11	32.4	3	326
Day31 to Day90 after transplantation	11	32.4	3	512
Day91 to Day180 after transplantation	10	29.4	2	768
> 180 days after transplantation	21	61.8	18	5397
> 30 days after Acute bacterial infection	26	76.5	26	7003

Table 127 Relative incidence of kidney transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and acute bacterial infections (Subset 1b)

No records exist in this table

Table 128 Kidney transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and chronic viral infections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	34	100.0	51	13007
Data after censoring according to transplantations	34	100.0	51	11071
Data after censoring according to second rejection	34	100.0	34	9626
Subjects with at least one exposure of interest (Chronic viral infection, Pandemrix, transplantation)	26	76.5	26	7003
Pandemrix - Control period before first dose	26	76.5	11	2495
Pandemrix - Risk period after dose 1	18	52.9	1	521
Pandemrix - Control period after dose 1	14	41.2	9	2698
Pandemrix - Risk period after dose 2	5	14.7	1	155
Pandemrix - Control period after dose 2	5	14.7	4	1134
Pandemrix - Pooled risk periods	18	52.9	2	676
Pandemrix - Pooled control periods	26	76.5	24	6327
Day0 to Day30 after transplantation	11	32.4	3	326
Day31 to Day90 after transplantation	11	32.4	3	512
Day91 to Day180 after transplantation	10	29.4	2	768
> 180 days after transplantation	21	61.8	18	5397
> 365 days after Chronic viral infection	26	76.5	26	7003

Table 129 Relative incidence of kidney transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and chronic viral infection (Subset 1b)

No records exist in this table

Table 130 Kidney transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and malignancies/cancers (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	34	100.0	51	13007
Data after censoring according to transplantations	34	100.0	51	11071
Data after censoring according to second rejection	34	100.0	34	9626
Subjects with at least one exposure of interest (Cancer, Pandemrix, transplantation)	26	76.5	26	7003
Pandemrix - Control period before first dose	26	76.5	11	2495
Pandemrix - Risk period after dose 1	18	52.9	1	521
Pandemrix - Control period after dose 1	14	41.2	9	2698
Pandemrix - Risk period after dose 2	5	14.7	1	155
Pandemrix - Control period after dose 2	5	14.7	4	1134
Pandemrix - Pooled risk periods	18	52.9	2	676
Pandemrix - Pooled control periods	26	76.5	24	6327
Day0 to Day30 after transplantation	11	32.4	3	326
Day31 to Day90 after transplantation	11	32.4	3	512
Day91 to Day180 after transplantation	10	29.4	2	768
> 180 days after transplantation	21	61.8	18	5397
> 365 days after Cancer	26	76.5	26	7003

Table 131 Relative incidence of kidney transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and malignancies/cancers (Subset 1b)

No records exist in this table

Table 132 Kidney transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and chemotherapy (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	34	100.0	51	13007
Data after censoring according to transplantations	34	100.0	51	11071
Data after censoring according to second rejection	34	100.0	34	9626
Subjects with at least one exposure of interest (Chemotherapy, Pandemrix, transplantation)	26	76.5	26	7003
Pandemrix - Control period before first dose	26	76.5	11	2495
Pandemrix - Risk period after dose 1	18	52.9	1	521
Pandemrix - Control period after dose 1	14	41.2	9	2698
Pandemrix - Risk period after dose 2	5	14.7	1	155
Pandemrix - Control period after dose 2	5	14.7	4	1134
Pandemrix - Pooled risk periods	18	52.9	2	676
Pandemrix - Pooled control periods	26	76.5	24	6327
Day0 to Day30 after transplantation	11	32.4	3	326
Day31 to Day90 after transplantation	11	32.4	3	512
Day91 to Day180 after transplantation	10	29.4	2	768
> 180 days after transplantation	21	61.8	18	5397
Day0 to Day365 after Chemotherapy	1	2.9	1	295
> 365 days after Chemotherapy	26	76.5	25	6708

Table 133 Relative incidence of kidney transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and chemotherapy (Subset 1b)

No records exist in this table

Table 134 Kidney transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and all covariates (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	34	100.0	51	13007
Data after censoring according to transplantations	34	100.0	51	11071
Data after censoring according to second rejection	34	100.0	34	9626
Subjects with at least one exposure of interest (Acute bacterial infection, Cancer, Chemotherapy, Chronic viral infection, Opportunistic infection, Pandemrix, Respiratory infection, Seasonal vaccine, transplantation)	29	85.3	29	8124
Pandemrix - Control period before first dose	29	85.3	14	3616
Pandemrix - Risk period after dose 1	18	52.9	1	521
Pandemrix - Control period after dose 1	14	41.2	9	2698
Pandemrix - Risk period after dose 2	5	14.7	1	155
Pandemrix - Control period after dose 2	5	14.7	4	1134
Pandemrix - Pooled risk periods	18	52.9	2	676
Pandemrix - Pooled control periods	29	85.3	27	7448
Day0 to Day30 after transplantation	11	32.4	3	326
Day31 to Day90 after transplantation	11	32.4	3	512
Day91 to Day180 after transplantation	10	29.4	2	768
> 180 days after transplantation	24	70.6	21	6518
Day0 to Day30 after Seasonal vaccine	16	47.1	1	552
> 30 days after Seasonal vaccine	29	85.3	28	7572
Day0 to Day30 after Respiratory infection	3	8.8	0	93
> 30 days after Respiratory infection	29	85.3	29	8031
Day0 to Day30 after Opportunistic infection	2	5.9	0	80
> 30 days after Opportunistic infection	29	85.3	29	8044
> 30 days after Acute bacterial infection	29	85.3	29	8124
> 365 days after Chronic viral infection	29	85.3	29	8124
> 365 days after Cancer	29	85.3	29	8124
Day0 to Day365 after Chemotherapy	1	2.9	1	295
> 365 days after Chemotherapy	29	85.3	28	7829

Table 135 Relative incidence of kidney transplant rejection within 30 days after Pandemrix vaccination adjusted for all covariates (Subset 1b)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	30 days after any dose vs. other periods	0.56	0.21	1.50
Time since transplantation	0-30 vs. >180 days	0.86	0.11	6.47
	31-90 vs. >180 days	1.51	0.29	7.85
	91-180 vs. >180 days	0.62	0.05	7.93
Seasonal influenza vaccination	30 days after vaccination vs. other periods	1.18	0.26	5.34

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 136 Kidney transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix and the time since transplantation – with subsequent rejections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	34	100.0	51	13007
Data after censoring according to transplantations	34	100.0	51	11071
Subjects with at least one exposure of interest (Pandemrix, transplantation)	26	76.5	35	7903
Pandemrix - Control period before first dose	26	76.5	13	2579
Pandemrix - Risk period after any dose	18	52.9	2	676
Pandemrix - Control period after any dose	18	52.9	20	4648
Pandemrix - Pooled risk periods	18	52.9	2	676
Pandemrix - Pooled control periods	26	76.5	33	7227
Day0 to Day30 after transplantation	11	32.4	3	326
Day31 to Day90 after transplantation	11	32.4	4	536
Day91 to Day180 after transplantation	10	29.4	2	768
> 180 days after transplantation	21	61.8	26	6273

Table 137 Relative incidence of kidney transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation - not accounting for perturbed post-event exposure (Subset 1b)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	30 days after any dose vs. other periods	0.72	0.16	3.21
Time since transplantation	0-30 vs. >180 days	0.40	0.05	3.31
	31-90 vs. >180 days	0.57	0.09	3.45
	91-180 vs. >180 days	0.36	0.06	2.24

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit

Table 138 Relative incidence of kidney transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and conditioned to previous rejections (Subset 1b)

No records exist in this table

Table 139 Kidney transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix and the time since transplantation - Subjects without previous rejections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	22	100.0	30	8324
Data after censoring according to transplantations	22	100.0	30	6388
Data after censoring according to second rejection	22	100.0	22	5676
Subjects with at least one exposure of interest (Pandemrix, transplantation)	22	100.0	22	5676
Pandemrix - Control period before first dose	22	100.0	11	2235
Pandemrix - Risk period after dose 1	14	63.6	0	397
Pandemrix - Control period after dose 1	10	45.5	6	1755
Pandemrix - Risk period after dose 2	5	22.7	1	155
Pandemrix - Control period after dose 2	5	22.7	4	1134
Pandemrix - Pooled risk periods	14	63.6	1	552
Pandemrix - Pooled control periods	22	100.0	21	5124
Day0 to Day30 after transplantation	10	45.5	3	310
Day31 to Day90 after transplantation	10	45.5	3	452
Day91 to Day180 after transplantation	8	36.4	1	595
> 180 days after transplantation	17	77.3	15	4319

Table 140 Relative incidence of kidney transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation - Subjects without previous rejections (Subset 1b)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	30 days after any dose vs. other periods	0.10	0.08	0.12
Time since transplantation	0-30 vs. >180 days	0.19	0.03	1.30
	31-90 vs. >180 days	0.73	0.17	3.05
	91-180 vs. >180 days	0.02	0.00	0.73

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 141 Kidney transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and previous rejection - Subjects with previous rejections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	4	100.0	5	1515
Data after censoring according to transplantations	4	100.0	5	1515
Data after censoring according to second rejection	4	100.0	4	1327
Subjects with at least one exposure of interest (Pandemrix, Previous rejection, transplantation)	4	100.0	4	1327
Pandemrix - Control period before first dose	4	100.0	0	260
Pandemrix - Risk period after dose 1	4	100.0	1	124
Pandemrix - Control period after dose 1	4	100.0	3	943
Pandemrix - Pooled risk periods	4	100.0	1	124
Pandemrix - Pooled control periods	4	100.0	3	1203
Day0 to Day30 after transplantation	1	25.0	0	16
Day31 to Day90 after transplantation	1	25.0	0	60
Day91 to Day180 after transplantation	2	50.0	1	173
> 180 days after transplantation	4	100.0	3	1078
Day0 to Day180 after Previous rejection	4	100.0	2	487
> 180 days after Previous rejection	3	75.0	2	840

Table 142 Relative incidence of kidney transplant rejection within 30 days after Pandemrix vaccination adjusted for the time since transplantation and previous rejection - Subjects with previous rejections (Subset 1b)

No records exist in this table

Table 143 Liver transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix and the time since transplantation (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	11	100.0	14	4356
Data after censoring according to transplantations	11	100.0	14	3359
Data after censoring according to second rejection	11	100.0	11	3241
Subjects with at least one exposure of interest (Pandemrix, transplantation)	8	72.7	8	2385
Pandemrix - Control period before first dose	8	72.7	6	1245
Pandemrix - Risk period after dose 1	4	36.4	1	116
Pandemrix - Control period after dose 1	3	27.3	1	751
Pandemrix - Risk period after dose 2	1	9.1	0	31
Pandemrix - Control period after dose 2	1	9.1	0	242
Pandemrix - Pooled risk periods	4	36.4	1	147
Pandemrix - Pooled control periods	8	72.7	7	2238
Day0 to Day30 after transplantation	4	36.4	3	124
Day31 to Day90 after transplantation	4	36.4	0	207
Day91 to Day180 after transplantation	5	45.5	0	397
> 180 days after transplantation	7	63.6	5	1657

Table 144 Liver transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix the time since transplantation and all covariates (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	10	100.0	13	3960
Data after censoring according to transplantations	10	100.0	13	3039
Data after censoring according to second rejection	10	100.0	10	2921
Subjects with at least one exposure of interest (Acute bacterial infection, Cancer, Chemotherapy, Chronic viral infection, Opportunistic infection, Pandemrix, Respiratory infection, Seasonal vaccine, transplantation)	9	90.0	9	2525
Pandemrix - Control period before first dose	9	90.0	7	1385
Pandemrix - Risk period after dose 1	4	40.0	1	116
Pandemrix - Control period after dose 1	3	30.0	1	751
Pandemrix - Risk period after dose 2	1	10.0	0	31
Pandemrix - Control period after dose 2	1	10.0	0	242
Pandemrix - Pooled risk periods	4	40.0	1	147
Pandemrix - Pooled control periods	9	90.0	8	2378
Day0 to Day30 after transplantation	3	30.0	2	93
Day31 to Day90 after transplantation	3	30.0	0	147
Day91 to Day180 after transplantation	4	40.0	0	307
> 180 days after transplantation	8	80.0	7	1978
Day0 to Day30 after Seasonal vaccine	4	40.0	0	124
> 30 days after Seasonal vaccine	9	90.0	9	2401
> 30 days after Respiratory infection	9	90.0	9	2525
> 30 days after Opportunistic infection	9	90.0	9	2525
> 30 days after Acute bacterial infection	9	90.0	9	2525
> 365 days after Chronic viral infection	9	90.0	9	2525
Day0 to Day365 after Cancer	1	10.0	1	315
> 365 days after Cancer	9	90.0	8	2210
Day0 to Day365 after Chemotherapy	3	30.0	2	750
> 365 days after Chemotherapy	8	80.0	7	1775

Table 145 Lung transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix and the time since transplantation (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	4	100.0	6	1508
Data after censoring according to transplantations	4	100.0	6	1274
Data after censoring according to second rejection	4	100.0	4	1044
Subjects with at least one exposure of interest (Pandemrix, transplantation)	3	75.0	3	724
Pandemrix - Control period before first dose	3	75.0	2	270
Pandemrix - Risk period after dose 1	2	50.0	0	41
Pandemrix - Risk period after dose 2	2	50.0	0	62
Pandemrix - Control period after dose 2	2	50.0	1	351
Pandemrix - Pooled risk periods	2	50.0	0	103
Pandemrix - Pooled control periods	3	75.0	3	621
Day0 to Day30 after transplantation	2	50.0	0	41
Day31 to Day90 after transplantation	2	50.0	2	120
Day91 to Day180 after transplantation	2	50.0	0	161
> 180 days after transplantation	2	50.0	1	402

Table 146 Pancreas transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 30-days risk periods of Pandemrix and the time since transplantation (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	1	100.0	1	208
Data after censoring according to transplantations	1	100.0	1	208
Data after censoring according to second rejection	1	100.0	1	208
Subjects with at least one exposure of interest (Pandemrix, transplantation)	1	100.0	1	208
Pandemrix - Control period before first dose	1	100.0	1	57
Pandemrix - Risk period after dose 1	1	100.0	0	31
Pandemrix - Control period after dose 1	1	100.0	0	120
Pandemrix - Pooled risk periods	1	100.0	0	31
Pandemrix - Pooled control periods	1	100.0	1	177
Day91 to Day180 after transplantation	1	100.0	0	15
> 180 days after transplantation	1	100.0	1	193

Table 147 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix and the time since transplantation (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	184	100.0	245	70378
Data after censoring according to transplantations	184	100.0	244	65276
Data after censoring according to second rejection	184	100.0	184	59836
Subjects with at least one exposure of interest (Pandemrix, transplantation)	91	49.5	91	27627
Pandemrix - Control period before first dose	90	48.9	34	8129
Pandemrix - Risk period after dose 1	72	39.1	12	3629
Pandemrix - Control period after dose 1	51	27.7	32	11252
Pandemrix - Risk period after dose 2	16	8.7	1	976
Pandemrix - Control period after dose 2	16	8.7	12	3641
Pandemrix - Pooled risk periods	72	39.1	13	4605
Pandemrix - Pooled control periods	91	49.5	78	23022
Day0 to Day30 after transplantation	23	12.5	10	640
Day31 to Day90 after transplantation	24	13.0	8	1154
Day91 to Day180 after transplantation	21	11.4	2	1668
> 180 days after transplantation	80	43.5	71	24165

Table 148 Relative incidence of SOT rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	60 days after any dose vs. other periods	0.80	0.42	1.50
Time since transplantation	0-30 vs. >180 days	4.47	1.02	19.68
	31-90 vs. >180 days	2.33	0.56	9.68
	91-180 vs. >180 days	0.41	0.06	2.76

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 149 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and seasonal vaccination (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	184	100.0	245	70378
Data after censoring according to transplantations	184	100.0	244	65276
Data after censoring according to second rejection	184	100.0	184	59836
Subjects with at least one exposure of interest (Pandemrix, Seasonal vaccine, transplantation)	119	64.7	119	37100
Pandemrix - Control period before first dose	118	64.1	62	17602
Pandemrix - Risk period after dose 1	72	39.1	12	3629
Pandemrix - Control period after dose 1	51	27.7	32	11252
Pandemrix - Risk period after dose 2	16	8.7	1	976
Pandemrix - Control period after dose 2	16	8.7	12	3641
Pandemrix - Pooled risk periods	72	39.1	13	4605
Pandemrix - Pooled control periods	119	64.7	106	32495
Day0 to Day30 after transplantation	23	12.5	10	640
Day31 to Day90 after transplantation	24	13.0	8	1154
Day91 to Day180 after transplantation	21	11.4	2	1668
> 180 days after transplantation	108	58.7	99	33638
Day0 to Day30 after Seasonal vaccine	94	51.1	6	3358
> 30 days after Seasonal vaccine	119	64.7	113	33742

Table 150 Relative incidence of SOT rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and seasonal vaccination (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	60 days after any dose vs. other periods	0.84	0.45	1.58
Time since transplantation	0-30 vs. >180 days	4.54	1.00	20.61
	31-90 vs. >180 days	2.36	0.55	10.21
	91-180 vs. >180 days	0.42	0.06	3.03
Seasonal influenza vaccination	30 days after vaccination vs. other periods	0.46	0.18	1.14

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 151 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and respiratory infections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	184	100.0	245	70378
Data after censoring according to transplantations	184	100.0	244	65276
Data after censoring according to second rejection	184	100.0	184	59836
Subjects with at least one exposure of interest (Pandemrix, Respiratory infection, transplantation)	91	49.5	91	27627
Pandemrix - Control period before first dose	90	48.9	34	8129
Pandemrix - Risk period after dose 1	72	39.1	12	3629
Pandemrix - Control period after dose 1	51	27.7	32	11252
Pandemrix - Risk period after dose 2	16	8.7	1	976
Pandemrix - Control period after dose 2	16	8.7	12	3641
Pandemrix - Pooled risk periods	72	39.1	13	4605
Pandemrix - Pooled control periods	91	49.5	78	23022
Day0 to Day30 after transplantation	23	12.5	10	640
Day31 to Day90 after transplantation	24	13.0	8	1154
Day91 to Day180 after transplantation	21	11.4	2	1668
> 180 days after transplantation	80	43.5	71	24165
Day0 to Day30 after Respiratory infection	2	1.1	0	62
> 30 days after Respiratory infection	91	49.5	91	27565

Table 152 Relative incidence of SOT rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and respiratory infections (Subset 1a)

No records exist in this table

Table 153 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and opportunistic infections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	184	100.0	245	70378
Data after censoring according to transplantations	184	100.0	244	65276
Data after censoring according to second rejection	184	100.0	184	59836
Subjects with at least one exposure of interest (Opportunistic infection, Pandemrix, transplantation)	92	50.0	92	28023
Pandemrix - Control period before first dose	91	49.5	35	8525
Pandemrix - Risk period after dose 1	72	39.1	12	3629
Pandemrix - Control period after dose 1	51	27.7	32	11252
Pandemrix - Risk period after dose 2	16	8.7	1	976
Pandemrix - Control period after dose 2	16	8.7	12	3641
Pandemrix - Pooled risk periods	72	39.1	13	4605
Pandemrix - Pooled control periods	92	50.0	79	23418
Day0 to Day30 after transplantation	23	12.5	10	640
Day31 to Day90 after transplantation	24	13.0	8	1154
Day91 to Day180 after transplantation	21	11.4	2	1668
> 180 days after transplantation	81	44.0	72	24561
Day0 to Day30 after Opportunistic infection	6	3.3	1	260
> 30 days after Opportunistic infection	92	50.0	91	27763

Table 154 Relative incidence of SOT rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and opportunistic infections (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	60 days after any dose vs. other periods	0.80	0.43	1.51
Time since transplantation	0-30 vs. >180 days	4.36	0.97	19.62
	31-90 vs. >180 days	2.30	0.54	9.78
	91-180 vs. >180 days	0.40	0.06	2.74
Opportunistic infections	30 days after infection vs. other periods	1.71	0.16	17.93

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 155 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and acute bacterial infections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	184	100.0	245	70378
Data after censoring according to transplantations	184	100.0	244	65276
Data after censoring according to second rejection	184	100.0	184	59836
Subjects with at least one exposure of interest (Acute bacterial infection, Pandemrix, transplantation)	91	49.5	91	27627
Pandemrix - Control period before first dose	90	48.9	34	8129
Pandemrix - Risk period after dose 1	72	39.1	12	3629
Pandemrix - Control period after dose 1	51	27.7	32	11252
Pandemrix - Risk period after dose 2	16	8.7	1	976
Pandemrix - Control period after dose 2	16	8.7	12	3641
Pandemrix - Pooled risk periods	72	39.1	13	4605
Pandemrix - Pooled control periods	91	49.5	78	23022
Day0 to Day30 after transplantation	23	12.5	10	640
Day31 to Day90 after transplantation	24	13.0	8	1154
Day91 to Day180 after transplantation	21	11.4	2	1668
> 180 days after transplantation	80	43.5	71	24165
> 30 days after Acute bacterial infection	91	49.5	91	27627

Table 156 Relative incidence of SOT rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and acute bacterial infections (Subset 1a)

No records exist in this table

Table 157 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and chronic viral infections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	178	100.0	239	68002
Data after censoring according to transplantations	178	100.0	238	62976
Data after censoring according to second rejection	178	100.0	178	57536
Subjects with at least one exposure of interest (Chronic viral infection, Pandemrix, transplantation)	88	49.4	88	26515
Pandemrix - Control period before first dose	87	48.9	32	7366
Pandemrix - Risk period after dose 1	71	39.9	12	3568
Pandemrix - Control period after dose 1	50	28.1	31	10964
Pandemrix - Risk period after dose 2	16	9.0	1	976
Pandemrix - Control period after dose 2	16	9.0	12	3641
Pandemrix - Pooled risk periods	71	39.9	13	4544
Pandemrix - Pooled control periods	88	49.4	75	21971
Day0 to Day30 after transplantation	21	11.8	9	603
Day31 to Day90 after transplantation	22	12.4	7	1034
Day91 to Day180 after transplantation	19	10.7	2	1488
> 180 days after transplantation	77	43.3	70	23390
> 365 days after Chronic viral infection	88	49.4	88	26515

Table 158 Relative incidence of SOT rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and chronic viral infection (Subset 1a)

No records exist in this table

Table 159 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and malignancies/cancers (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	178	100.0	239	68002
Data after censoring according to transplantations	178	100.0	238	62976
Data after censoring according to second rejection	178	100.0	178	57536
Subjects with at least one exposure of interest (Cancer, Pandemrix, transplantation)	93	52.2	93	28376
Pandemrix - Control period before first dose	92	51.7	37	9227
Pandemrix - Risk period after dose 1	71	39.9	12	3568
Pandemrix - Control period after dose 1	50	28.1	31	10964
Pandemrix - Risk period after dose 2	16	9.0	1	976
Pandemrix - Control period after dose 2	16	9.0	12	3641
Pandemrix - Pooled risk periods	71	39.9	13	4544
Pandemrix - Pooled control periods	93	52.2	80	23832
Day0 to Day30 after transplantation	21	11.8	9	603
Day31 to Day90 after transplantation	22	12.4	7	1034
Day91 to Day180 after transplantation	19	10.7	2	1488
> 180 days after transplantation	82	46.1	75	25251
Day0 to Day365 after Cancer	15	8.4	11	3103
> 365 days after Cancer	93	52.2	82	25273

Table 160 Relative incidence of SOT rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and malignancies/cancers (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	60 days after any dose vs. other periods	0.85	0.45	1.60
Time since transplantation	0-30 vs. >180 days	2.77	0.58	13.32
	31-90 vs. >180 days	1.53	0.33	7.04
	91-180 vs. >180 days	0.33	0.04	2.54
Malignancies/ cancers	365 days after any record vs. other periods	3.47	0.86	14.00

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 161 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and all covariates (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	178	100.0	239	68002
Data after censoring according to transplantations	178	100.0	238	62976
Data after censoring according to second rejection	178	100.0	178	57536
Subjects with at least one exposure of interest (Acute bacterial infection, Cancer, Chronic viral infection, Opportunistic infection, Pandemrix, Respiratory infection, Seasonal vaccine, transplantation)	120	67.4	120	37453
Pandemrix - Control period before first dose	119	66.9	64	18304
Pandemrix - Risk period after dose 1	71	39.9	12	3568
Pandemrix - Control period after dose 1	50	28.1	31	10964
Pandemrix - Risk period after dose 2	16	9.0	1	976
Pandemrix - Control period after dose 2	16	9.0	12	3641
Pandemrix - Pooled risk periods	71	39.9	13	4544
Pandemrix - Pooled control periods	120	67.4	107	32909
Day0 to Day30 after transplantation	21	11.8	9	603
Day31 to Day90 after transplantation	22	12.4	7	1034
Day91 to Day180 after transplantation	19	10.7	2	1488
> 180 days after transplantation	109	61.2	102	34328
Day0 to Day30 after Seasonal vaccine	92	51.7	5	3273
> 30 days after Seasonal vaccine	120	67.4	115	34180
Day0 to Day30 after Respiratory infection	2	1.1	0	62
> 30 days after Respiratory infection	120	67.4	120	37391
Day0 to Day30 after Opportunistic infection	6	3.4	1	260
> 30 days after Opportunistic infection	120	67.4	119	37193
> 30 days after Acute bacterial infection	120	67.4	120	37453
> 365 days after Chronic viral infection	120	67.4	120	37453
Day0 to Day365 after Cancer	15	8.4	11	3103
> 365 days after Cancer	120	67.4	109	34350

Table 162 Relative incidence of SOT rejection within 60 days after Pandemrix vaccination adjusted for all covariates (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	60 days after any dose vs. other periods	0.91	0.49	1.70
Time since transplantation	0-30 vs. >180 days	2.72	0.54	13.70
	31-90 vs. >180 days	1.51	0.31	7.30
	91-180 vs. >180 days	0.34	0.04	2.78
Seasonal influenza vaccination	30 days after vaccination vs. other periods	0.40	0.15	1.08
Opportunistic infections	30 days after infection vs. other periods	1.78	0.17	18.72
Malignancies/ cancers	365 days after any record vs. other periods	3.34	0.82	13.56

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 163 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix and the time since transplantation – with subsequent rejections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	184	100.0	245	70378
Data after censoring according to transplantations	184	100.0	244	65276
Subjects with at least one exposure of interest (Pandemrix, transplantation)	91	49.5	129	31130
Pandemrix - Control period before first dose	90	48.9	41	8355
Pandemrix - Risk period after any dose	73	39.7	18	4871
Pandemrix - Control period after any dose	73	39.7	70	17904
Pandemrix - Pooled risk periods	73	39.7	18	4871
Pandemrix - Pooled control periods	91	49.5	111	26259
Day0 to Day30 after transplantation	23	12.5	10	640
Day31 to Day90 after transplantation	24	13.0	11	1238
Day91 to Day180 after transplantation	23	12.5	2	1776
> 180 days after transplantation	81	44.0	106	27476

Table 164 Relative incidence of SOT rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation - not accounting for perturbed post-event exposure (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	60 days after any dose vs. other periods	0.96	0.58	1.61
Time since transplantation	0-30 vs. >180 days	2.14	0.71	6.43
	31-90 vs. >180 days	1.47	0.54	4.00
	91-180 vs. >180 days	0.23	0.05	1.06

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit

Table 165 Relative incidence of SOT rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and conditioned to previous rejections (Subset 1a)

No records exist in this table

Table 166 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix and the time since transplantation - subjects without previous rejections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	82	100.0	111	31597
Data after censoring according to transplantations	82	100.0	111	27771
Data after censoring according to second rejection	82	100.0	82	25425
Subjects with at least one exposure of interest (Pandemrix, transplantation)	82	100.0	82	25425
Pandemrix - Control period before first dose	81	98.8	31	7518
Pandemrix - Risk period after dose 1	63	76.8	10	3164
Pandemrix - Control period after dose 1	45	54.9	29	10326
Pandemrix - Risk period after dose 2	15	18.3	1	915
Pandemrix - Control period after dose 2	15	18.3	11	3502
Pandemrix - Pooled risk periods	63	76.8	11	4079
Pandemrix - Pooled control periods	82	100.0	71	21346
Day0 to Day30 after transplantation	21	25.6	10	614
Day31 to Day90 after transplantation	22	26.8	8	1034
Day91 to Day180 after transplantation	17	20.7	1	1316
> 180 days after transplantation	71	86.6	63	22461

Table 167 Relative incidence of SOT rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation - Subjects without previous rejections (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	60 days after any dose vs. other periods	0.74	0.37	1.48
Time since transplantation	0-30 vs. >180 days	5.09	0.87	29.74
	31-90 vs. >180 days	2.73	0.50	14.90
	91-180 vs. >180 days	0.18	0.02	1.85

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 168 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and previous rejection - Subjects with previous rejections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	9	100.0	18	3495
Data after censoring according to transplantations	9	100.0	18	3359
Data after censoring according to second rejection	9	100.0	9	2202
Subjects with at least one exposure of interest (Pandemrix, Previous rejection, transplantation)	9	100.0	9	2202
Pandemrix - Control period before first dose	9	100.0	3	611
Pandemrix - Risk period after dose 1	9	100.0	2	465
Pandemrix - Control period after dose 1	6	66.7	3	926
Pandemrix - Risk period after dose 2	1	11.1	0	61
Pandemrix - Control period after dose 2	1	11.1	1	139
Pandemrix - Pooled risk periods	9	100.0	2	526
Pandemrix - Pooled control periods	9	100.0	7	1676
Day0 to Day30 after transplantation	2	22.2	0	26
Day31 to Day90 after transplantation	2	22.2	0	120
Day91 to Day180 after transplantation	4	44.4	1	352
> 180 days after transplantation	9	100.0	8	1704
Day0 to Day180 after Previous rejection	9	100.0	5	927
> 180 days after Previous rejection	6	66.7	4	1275

Table 169 Relative incidence of SOT rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and previous rejection - Subjects with previous rejections (Subset 1a)

No records exist in this table

Table 170 Heart transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix and the time since transplantation (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	8	100.0	9	2953
Data after censoring according to transplantations	8	100.0	9	2803
Data after censoring according to second rejection	8	100.0	8	2703
Subjects with at least one exposure of interest (Pandemrix, transplantation)	4	50.0	4	1219
Pandemrix - Control period before first dose	4	50.0	1	215
Pandemrix - Risk period after dose 1	4	50.0	1	244
Pandemrix - Control period after dose 1	4	50.0	2	760
Pandemrix - Pooled risk periods	4	50.0	1	244
Pandemrix - Pooled control periods	4	50.0	3	975
> 180 days after transplantation	4	50.0	4	1219

Table 171 Kidney transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix and the time since transplantation (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	97	100.0	145	36917
Data after censoring according to transplantations	97	100.0	145	33766
Data after censoring according to second rejection	97	100.0	97	29510
Subjects with at least one exposure of interest (Pandemrix, transplantation)	65	67.0	65	19565
Pandemrix - Control period before first dose	65	67.0	24	5478
Pandemrix - Risk period after dose 1	53	54.6	8	2676
Pandemrix - Control period after dose 1	36	37.1	23	7918
Pandemrix - Risk period after dose 2	12	12.4	1	732
Pandemrix - Control period after dose 2	12	12.4	9	2761
Pandemrix - Pooled risk periods	53	54.6	9	3408
Pandemrix - Pooled control periods	65	67.0	56	16157
Day0 to Day30 after transplantation	15	15.5	6	425
Day31 to Day90 after transplantation	16	16.5	5	744
Day91 to Day180 after transplantation	14	14.4	2	1110
> 180 days after transplantation	58	59.8	52	17286

Table 172 Relative incidence of kidney transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	60 days after any dose vs. other periods	0.68	0.33	1.40
Time since transplantation	0-30 vs. >180 days	3.86	0.54	27.29
	31-90 vs. >180 days	2.95	0.47	18.71
	91-180 vs. >180 days	0.83	0.08	8.40

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 173 Kidney transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and seasonal vaccination (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	97	100.0	145	36917
Data after censoring according to transplantations	97	100.0	145	33766
Data after censoring according to second rejection	97	100.0	97	29510
Subjects with at least one exposure of interest (Pandemrix, Seasonal vaccine, transplantation)	73	75.3	73	22135
Pandemrix - Control period before first dose	73	75.3	32	8048
Pandemrix - Risk period after dose 1	53	54.6	8	2676
Pandemrix - Control period after dose 1	36	37.1	23	7918
Pandemrix - Risk period after dose 2	12	12.4	1	732
Pandemrix - Control period after dose 2	12	12.4	9	2761
Pandemrix - Pooled risk periods	53	54.6	9	3408
Pandemrix - Pooled control periods	73	75.3	64	18727
Day0 to Day30 after transplantation	15	15.5	6	425
Day31 to Day90 after transplantation	16	16.5	5	744
Day91 to Day180 after transplantation	14	14.4	2	1110
> 180 days after transplantation	66	68.0	60	19856
Day0 to Day30 after Seasonal vaccine	58	59.8	5	1997
> 30 days after Seasonal vaccine	73	75.3	68	20138

Table 174 Relative incidence of kidney transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and seasonal vaccination (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	60 days after any dose vs. other periods	0.71	0.34	1.46
Time since transplantation	0-30 vs. >180 days	3.91	0.52	29.45
	31-90 vs. >180 days	2.98	0.43	20.37
	91-180 vs. >180 days	0.84	0.07	9.53
Seasonal influenza vaccination	30 days after vaccination vs. other periods	0.63	0.22	1.83

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 175 Kidney transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and respiratory infections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	97	100.0	145	36917
Data after censoring according to transplantations	97	100.0	145	33766
Data after censoring according to second rejection	97	100.0	97	29510
Subjects with at least one exposure of interest (Pandemrix, Respiratory infection, transplantation)	65	67.0	65	19565
Pandemrix - Control period before first dose	65	67.0	24	5478
Pandemrix - Risk period after dose 1	53	54.6	8	2676
Pandemrix - Control period after dose 1	36	37.1	23	7918
Pandemrix - Risk period after dose 2	12	12.4	1	732
Pandemrix - Control period after dose 2	12	12.4	9	2761
Pandemrix - Pooled risk periods	53	54.6	9	3408
Pandemrix - Pooled control periods	65	67.0	56	16157
Day0 to Day30 after transplantation	15	15.5	6	425
Day31 to Day90 after transplantation	16	16.5	5	744
Day91 to Day180 after transplantation	14	14.4	2	1110
> 180 days after transplantation	58	59.8	52	17286
Day0 to Day30 after Respiratory infection	1	1.0	0	31
> 30 days after Respiratory infection	65	67.0	65	19534

Table 176 Relative incidence of kidney transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and respiratory infections (Subset 1a)

No records exist in this table

Table 177 Kidney transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and opportunistic infections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	97	100.0	145	36917
Data after censoring according to transplantations	97	100.0	145	33766
Data after censoring according to second rejection	97	100.0	97	29510
Subjects with at least one exposure of interest (Opportunistic infection, Pandemrix, transplantation)	65	67.0	65	19565
Pandemrix - Control period before first dose	65	67.0	24	5478
Pandemrix - Risk period after dose 1	53	54.6	8	2676
Pandemrix - Control period after dose 1	36	37.1	23	7918
Pandemrix - Risk period after dose 2	12	12.4	1	732
Pandemrix - Control period after dose 2	12	12.4	9	2761
Pandemrix - Pooled risk periods	53	54.6	9	3408
Pandemrix - Pooled control periods	65	67.0	56	16157
Day0 to Day30 after transplantation	15	15.5	6	425
Day31 to Day90 after transplantation	16	16.5	5	744
Day91 to Day180 after transplantation	14	14.4	2	1110
> 180 days after transplantation	58	59.8	52	17286
Day0 to Day30 after Opportunistic infection	4	4.1	1	165
> 30 days after Opportunistic infection	65	67.0	64	19400

Table 178 Relative incidence of kidney transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and opportunistic infections (Subset 1a)

No records exist in this table

Table 179 Kidney transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and acute bacterial infections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	97	100.0	145	36917
Data after censoring according to transplantations	97	100.0	145	33766
Data after censoring according to second rejection	97	100.0	97	29510
Subjects with at least one exposure of interest (Acute bacterial infection, Pandemrix, transplantation)	65	67.0	65	19565
Pandemrix - Control period before first dose	65	67.0	24	5478
Pandemrix - Risk period after dose 1	53	54.6	8	2676
Pandemrix - Control period after dose 1	36	37.1	23	7918
Pandemrix - Risk period after dose 2	12	12.4	1	732
Pandemrix - Control period after dose 2	12	12.4	9	2761
Pandemrix - Pooled risk periods	53	54.6	9	3408
Pandemrix - Pooled control periods	65	67.0	56	16157
Day0 to Day30 after transplantation	15	15.5	6	425
Day31 to Day90 after transplantation	16	16.5	5	744
Day91 to Day180 after transplantation	14	14.4	2	1110
> 180 days after transplantation	58	59.8	52	17286
> 30 days after Acute bacterial infection	65	67.0	65	19565

Table 180 Relative incidence of kidney transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and acute bacterial infections (Subset 1a)

No records exist in this table

Table 181 Kidney transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and chronic viral infections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	94	100.0	142	35729
Data after censoring according to transplantations	94	100.0	142	32578
Data after censoring according to second rejection	94	100.0	94	28322
Subjects with at least one exposure of interest (Chronic viral infection, Pandemrix, transplantation)	63	67.0	63	18773
Pandemrix - Control period before first dose	63	67.0	23	5035
Pandemrix - Risk period after dose 1	52	55.3	8	2615
Pandemrix - Control period after dose 1	35	37.2	22	7630
Pandemrix - Risk period after dose 2	12	12.8	1	732
Pandemrix - Control period after dose 2	12	12.8	9	2761
Pandemrix - Pooled risk periods	52	55.3	9	3347
Pandemrix - Pooled control periods	63	67.0	54	15426
Day0 to Day30 after transplantation	14	14.9	6	419
Day31 to Day90 after transplantation	15	16.0	4	684
Day91 to Day180 after transplantation	13	13.8	2	1020
> 180 days after transplantation	56	59.6	51	16650
> 365 days after Chronic viral infection	63	67.0	63	18773

Table 182 Relative incidence of kidney transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and chronic viral infection (Subset 1a)

No records exist in this table

Table 183 Kidney transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and malignancies/cancers (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	94	100.0	142	35729
Data after censoring according to transplantations	94	100.0	142	32578
Data after censoring according to second rejection	94	100.0	94	28322
Subjects with at least one exposure of interest (Cancer, Pandemrix, transplantation)	64	68.1	64	19169
Pandemrix - Control period before first dose	64	68.1	24	5431
Pandemrix - Risk period after dose 1	52	55.3	8	2615
Pandemrix - Control period after dose 1	35	37.2	22	7630
Pandemrix - Risk period after dose 2	12	12.8	1	732
Pandemrix - Control period after dose 2	12	12.8	9	2761
Pandemrix - Pooled risk periods	52	55.3	9	3347
Pandemrix - Pooled control periods	64	68.1	55	15822
Day0 to Day30 after transplantation	14	14.9	6	419
Day31 to Day90 after transplantation	15	16.0	4	684
Day91 to Day180 after transplantation	13	13.8	2	1020
> 180 days after transplantation	57	60.6	52	17046
Day0 to Day365 after Cancer	6	6.4	4	1444
> 365 days after Cancer	64	68.1	60	17725

Table 184 Relative incidence of kidney transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and malignancies/cancers (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	60 days after any dose vs. other periods	0.71	0.34	1.47
Time since transplantation	0-30 vs. >180 days	3.08	0.42	22.71
	31-90 vs. >180 days	2.13	0.31	14.81
	91-180 vs. >180 days	0.71	0.06	8.21
Malignancies/ cancers	365 days after any record vs. other periods	1.64	0.42	6.39

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 185 Kidney transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and all covariates (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	94	100.0	142	35729
Data after censoring according to transplantations	94	100.0	142	32578
Data after censoring according to second rejection	94	100.0	94	28322
Subjects with at least one exposure of interest (Acute bacterial infection, Cancer, Chronic viral infection, Opportunistic infection, Pandemrix, Respiratory infection, Seasonal vaccine, transplantation)	71	75.5	71	21343
Pandemrix - Control period before first dose	71	75.5	31	7605
Pandemrix - Risk period after dose 1	52	55.3	8	2615
Pandemrix - Control period after dose 1	35	37.2	22	7630
Pandemrix - Risk period after dose 2	12	12.8	1	732
Pandemrix - Control period after dose 2	12	12.8	9	2761
Pandemrix - Pooled risk periods	52	55.3	9	3347
Pandemrix - Pooled control periods	71	75.5	62	17996
Day0 to Day30 after transplantation	14	14.9	6	419
Day31 to Day90 after transplantation	15	16.0	4	684
Day91 to Day180 after transplantation	13	13.8	2	1020
> 180 days after transplantation	64	68.1	59	19220
Day0 to Day30 after Seasonal vaccine	56	59.6	4	1912
> 30 days after Seasonal vaccine	71	75.5	67	19431
Day0 to Day30 after Respiratory infection	1	1.1	0	31
> 30 days after Respiratory infection	71	75.5	71	21312
Day0 to Day30 after Opportunistic infection	4	4.3	1	165
> 30 days after Opportunistic infection	71	75.5	70	21178
> 30 days after Acute bacterial infection	71	75.5	71	21343
> 365 days after Chronic viral infection	71	75.5	71	21343
Day0 to Day365 after Cancer	6	6.4	4	1444
> 365 days after Cancer	71	75.5	67	19899

Table 186 Relative incidence of kidney transplant rejection within 60 days after Pandemrix vaccination adjusted for all covariates (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	60 days after any dose vs. other periods	0.75	0.37	1.55
Time since transplantation	0-30 vs. >180 days	3.10	0.40	24.17
	31-90 vs. >180 days	2.11	0.29	15.57
	91-180 vs. >180 days	0.72	0.06	9.25
Seasonal influenza vaccination	30 days after vaccination vs. other periods	0.54	0.17	1.71
Malignancies/ cancers	365 days after any record vs. other periods	1.55	0.41	5.90

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 187 Kidney transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix and the time since transplantation – with subsequent rejections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	97	100.0	145	36917
Data after censoring according to transplantations	97	100.0	145	33766
Subjects with at least one exposure of interest (Pandemrix, transplantation)	65	67.0	96	22490
Pandemrix - Control period before first dose	65	67.0	26	5562
Pandemrix - Risk period after any dose	53	54.6	14	3613
Pandemrix - Control period after any dose	53	54.6	56	13315
Pandemrix - Pooled risk periods	53	54.6	14	3613
Pandemrix - Pooled control periods	65	67.0	82	18877
Day0 to Day30 after transplantation	15	15.5	6	425
Day31 to Day90 after transplantation	16	16.5	6	768
Day91 to Day180 after transplantation	14	14.4	2	1110
> 180 days after transplantation	58	59.8	82	20187

Table 188 Relative incidence of kidney transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation - not accounting for perturbed post-event exposure (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	60 days after any dose vs. other periods	0.95	0.53	1.69
Time since transplantation	0-30 vs. >180 days	2.24	0.45	11.04
	31-90 vs. >180 days	1.70	0.40	7.22
	91-180 vs. >180 days	0.51	0.09	2.86

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit

Table 189 Relative incidence of kidney transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and conditioned to previous rejections (Subset 1a)

No records exist in this table

Table 190 Kidney transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix and the time since transplantation - Subjects without previous rejections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	58	100.0	81	22308
Data after censoring according to transplantations	58	100.0	81	19787
Data after censoring according to second rejection	58	100.0	58	17907
Subjects with at least one exposure of interest (Pandemrix, transplantation)	58	100.0	58	17907
Pandemrix - Control period before first dose	58	100.0	21	5030
Pandemrix - Risk period after dose 1	46	79.3	6	2292
Pandemrix - Control period after dose 1	31	53.4	21	7092
Pandemrix - Risk period after dose 2	12	20.7	1	732
Pandemrix - Control period after dose 2	12	20.7	9	2761
Pandemrix - Pooled risk periods	46	79.3	7	3024
Pandemrix - Pooled control periods	58	100.0	51	14883
Day0 to Day30 after transplantation	14	24.1	6	409
Day31 to Day90 after transplantation	15	25.9	5	684
Day91 to Day180 after transplantation	12	20.7	1	937
> 180 days after transplantation	51	87.9	46	15877

Table 191 Relative incidence of kidney transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation - Subjects without previous rejections (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	60 days after any dose vs. other periods	0.52	0.22	1.24
Time since transplantation	0-30 vs. >180 days	2.41	0.33	17.52
	31-90 vs. >180 days	1.96	0.29	13.08
	91-180 vs. >180 days	0.16	0.01	2.43

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 192 Kidney transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and previous rejection - Subjects with previous rejections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	7	100.0	15	2703
Data after censoring according to transplantations	7	100.0	15	2703
Data after censoring according to second rejection	7	100.0	7	1658
Subjects with at least one exposure of interest (Pandemrix, Previous rejection, transplantation)	7	100.0	7	1658
Pandemrix - Control period before first dose	7	100.0	3	448
Pandemrix - Risk period after dose 1	7	100.0	2	384
Pandemrix - Control period after dose 1	5	71.4	2	826
Pandemrix - Pooled risk periods	7	100.0	2	384
Pandemrix - Pooled control periods	7	100.0	5	1274
Day0 to Day30 after transplantation	1	14.3	0	16
Day31 to Day90 after transplantation	1	14.3	0	60
Day91 to Day180 after transplantation	2	28.6	1	173
> 180 days after transplantation	7	100.0	6	1409
Day0 to Day180 after Previous rejection	7	100.0	5	750
> 180 days after Previous rejection	4	57.1	2	908

Table 193 Relative incidence of kidney transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and previous rejection - Subjects with previous rejections (Subset 1a)

No records exist in this table

Table 194 Liver transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix and the time since transplantation (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	19	100.0	25	7524
Data after censoring according to transplantations	19	100.0	24	6190
Data after censoring according to second rejection	19	100.0	19	5827
Subjects with at least one exposure of interest (Pandemrix, transplantation)	12	63.2	12	3637
Pandemrix - Control period before first dose	11	57.9	7	1780
Pandemrix - Risk period after dose 1	7	36.8	2	337
Pandemrix - Control period after dose 1	6	31.6	3	1247
Pandemrix - Risk period after dose 2	1	5.3	0	61
Pandemrix - Control period after dose 2	1	5.3	0	212
Pandemrix - Pooled risk periods	7	36.8	2	398
Pandemrix - Pooled control periods	12	63.2	10	3239
Day0 to Day30 after transplantation	6	31.6	4	174
Day31 to Day90 after transplantation	6	31.6	1	300
Day91 to Day180 after transplantation	6	31.6	0	487
> 180 days after transplantation	10	52.6	7	2676

Table 195 Relative incidence of liver transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation (Subset 1a)

No records exist in this table

Table 196 Liver transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and seasonal vaccination (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	19	100.0	25	7524
Data after censoring according to transplantations	19	100.0	24	6190
Data after censoring according to second rejection	19	100.0	19	5827
Subjects with at least one exposure of interest (Pandemrix, Seasonal vaccine, transplantation)	13	68.4	13	3701
Pandemrix - Control period before first dose	12	63.2	8	1844
Pandemrix - Risk period after dose 1	7	36.8	2	337
Pandemrix - Control period after dose 1	6	31.6	3	1247
Pandemrix - Risk period after dose 2	1	5.3	0	61
Pandemrix - Control period after dose 2	1	5.3	0	212
Pandemrix - Pooled risk periods	7	36.8	2	398
Pandemrix - Pooled control periods	13	68.4	11	3303
Day0 to Day30 after transplantation	6	31.6	4	174
Day31 to Day90 after transplantation	6	31.6	1	300
Day91 to Day180 after transplantation	6	31.6	0	487
> 180 days after transplantation	11	57.9	8	2740
Day0 to Day30 after Seasonal vaccine	6	31.6	0	220
> 30 days after Seasonal vaccine	13	68.4	13	3481

Table 197 Relative incidence of liver transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and seasonal vaccination (Subset 1a)

No records exist in this table

Table 198 Liver transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and respiratory infections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	19	100.0	25	7524
Data after censoring according to transplantations	19	100.0	24	6190
Data after censoring according to second rejection	19	100.0	19	5827
Subjects with at least one exposure of interest (Pandemrix, Respiratory infection, transplantation)	12	63.2	12	3637
Pandemrix - Control period before first dose	11	57.9	7	1780
Pandemrix - Risk period after dose 1	7	36.8	2	337
Pandemrix - Control period after dose 1	6	31.6	3	1247
Pandemrix - Risk period after dose 2	1	5.3	0	61
Pandemrix - Control period after dose 2	1	5.3	0	212
Pandemrix - Pooled risk periods	7	36.8	2	398
Pandemrix - Pooled control periods	12	63.2	10	3239
Day0 to Day30 after transplantation	6	31.6	4	174
Day31 to Day90 after transplantation	6	31.6	1	300
Day91 to Day180 after transplantation	6	31.6	0	487
> 180 days after transplantation	10	52.6	7	2676
> 30 days after Respiratory infection	12	63.2	12	3637

Table 199 Relative incidence of liver transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and respiratory infections (Subset 1a)

No records exist in this table

Table 200 Liver transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and opportunistic infections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	19	100.0	25	7524
Data after censoring according to transplantations	19	100.0	24	6190
Data after censoring according to second rejection	19	100.0	19	5827
Subjects with at least one exposure of interest (Opportunistic infection, Pandemrix, transplantation)	12	63.2	12	3637
Pandemrix - Control period before first dose	11	57.9	7	1780
Pandemrix - Risk period after dose 1	7	36.8	2	337
Pandemrix - Control period after dose 1	6	31.6	3	1247
Pandemrix - Risk period after dose 2	1	5.3	0	61
Pandemrix - Control period after dose 2	1	5.3	0	212
Pandemrix - Pooled risk periods	7	36.8	2	398
Pandemrix - Pooled control periods	12	63.2	10	3239
Day0 to Day30 after transplantation	6	31.6	4	174
Day31 to Day90 after transplantation	6	31.6	1	300
Day91 to Day180 after transplantation	6	31.6	0	487
> 180 days after transplantation	10	52.6	7	2676
> 30 days after Opportunistic infection	12	63.2	12	3637

Table 201 Relative incidence of liver transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and opportunistic infections (Subset 1a)

No records exist in this table

Table 202 Liver transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and acute bacterial infections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	19	100.0	25	7524
Data after censoring according to transplantations	19	100.0	24	6190
Data after censoring according to second rejection	19	100.0	19	5827
Subjects with at least one exposure of interest (Acute bacterial infection, Pandemrix, transplantation)	12	63.2	12	3637
Pandemrix - Control period before first dose	11	57.9	7	1780
Pandemrix - Risk period after dose 1	7	36.8	2	337
Pandemrix - Control period after dose 1	6	31.6	3	1247
Pandemrix - Risk period after dose 2	1	5.3	0	61
Pandemrix - Control period after dose 2	1	5.3	0	212
Pandemrix - Pooled risk periods	7	36.8	2	398
Pandemrix - Pooled control periods	12	63.2	10	3239
Day0 to Day30 after transplantation	6	31.6	4	174
Day31 to Day90 after transplantation	6	31.6	1	300
Day91 to Day180 after transplantation	6	31.6	0	487
> 180 days after transplantation	10	52.6	7	2676
> 30 days after Acute bacterial infection	12	63.2	12	3637

Table 203 Relative incidence of liver transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and acute bacterial infections (Subset 1a)

No records exist in this table

Table 204 Liver transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and chronic viral infections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	18	100.0	24	7128
Data after censoring according to transplantations	18	100.0	23	5870
Data after censoring according to second rejection	18	100.0	18	5507
Subjects with at least one exposure of interest (Chronic viral infection, Pandemrix, transplantation)	11	61.1	11	3317
Pandemrix - Control period before first dose	10	55.6	6	1460
Pandemrix - Risk period after dose 1	7	38.9	2	337
Pandemrix - Control period after dose 1	6	33.3	3	1247
Pandemrix - Risk period after dose 2	1	5.6	0	61
Pandemrix - Control period after dose 2	1	5.6	0	212
Pandemrix - Pooled risk periods	7	38.9	2	398
Pandemrix - Pooled control periods	11	61.1	9	2919
Day0 to Day30 after transplantation	5	27.8	3	143
Day31 to Day90 after transplantation	5	27.8	1	240
Day91 to Day180 after transplantation	5	27.8	0	397
> 180 days after transplantation	9	50.0	7	2537
> 365 days after Chronic viral infection	11	61.1	11	3317

Table 205 Relative incidence of liver transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and chronic viral infection (Subset 1a)

No records exist in this table

Table 206 Liver transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and malignancies/cancers (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	18	100.0	24	7128
Data after censoring according to transplantations	18	100.0	23	5870
Data after censoring according to second rejection	18	100.0	18	5507
Subjects with at least one exposure of interest (Cancer, Pandemrix, transplantation)	12	66.7	12	3713
Pandemrix - Control period before first dose	11	61.1	7	1856
Pandemrix - Risk period after dose 1	7	38.9	2	337
Pandemrix - Control period after dose 1	6	33.3	3	1247
Pandemrix - Risk period after dose 2	1	5.6	0	61
Pandemrix - Control period after dose 2	1	5.6	0	212
Pandemrix - Pooled risk periods	7	38.9	2	398
Pandemrix - Pooled control periods	12	66.7	10	3315
Day0 to Day30 after transplantation	5	27.8	3	143
Day31 to Day90 after transplantation	5	27.8	1	240
Day91 to Day180 after transplantation	5	27.8	0	397
> 180 days after transplantation	10	55.6	8	2933
Day0 to Day365 after Cancer	3	16.7	2	541
> 365 days after Cancer	12	66.7	10	3172

Table 207 Relative incidence of liver transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and malignancies/cancers (Subset 1a)

No records exist in this table

Table 208 Liver transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and all covariates (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	18	100.0	24	7128
Data after censoring according to transplantations	18	100.0	23	5870
Data after censoring according to second rejection	18	100.0	18	5507
Subjects with at least one exposure of interest (Acute bacterial infection, Cancer, Chronic viral infection, Opportunistic infection, Pandemrix, Respiratory infection, Seasonal vaccine, transplantation)	13	72.2	13	3777
Pandemrix - Control period before first dose	12	66.7	8	1920
Pandemrix - Risk period after dose 1	7	38.9	2	337
Pandemrix - Control period after dose 1	6	33.3	3	1247
Pandemrix - Risk period after dose 2	1	5.6	0	61
Pandemrix - Control period after dose 2	1	5.6	0	212
Pandemrix - Pooled risk periods	7	38.9	2	398
Pandemrix - Pooled control periods	13	72.2	11	3379
Day0 to Day30 after transplantation	5	27.8	3	143
Day31 to Day90 after transplantation	5	27.8	1	240
Day91 to Day180 after transplantation	5	27.8	0	397
> 180 days after transplantation	11	61.1	9	2997
Day0 to Day30 after Seasonal vaccine	6	33.3	0	220
> 30 days after Seasonal vaccine	13	72.2	13	3557
> 30 days after Respiratory infection	13	72.2	13	3777
> 30 days after Opportunistic infection	13	72.2	13	3777
> 30 days after Acute bacterial infection	13	72.2	13	3777
> 365 days after Chronic viral infection	13	72.2	13	3777
Day0 to Day365 after Cancer	3	16.7	2	541
> 365 days after Cancer	13	72.2	11	3236

Table 209 Relative incidence of liver transplant rejection within 60 days after Pandemrix vaccination adjusted for all covariates (Subset 1a)

No records exist in this table

Table 210 Liver transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix and the time since transplantation – with subsequent rejections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	19	100.0	25	7524
Data after censoring according to transplantations	19	100.0	24	6190
Subjects with at least one exposure of interest (Pandemrix, transplantation)	12	63.2	16	3928
Pandemrix - Control period before first dose	11	57.9	10	1898
Pandemrix - Risk period after any dose	7	36.8	2	398
Pandemrix - Control period after any dose	7	36.8	4	1632
Pandemrix - Pooled risk periods	7	36.8	2	398
Pandemrix - Pooled control periods	12	63.2	14	3530
Day0 to Day30 after transplantation	6	31.6	4	174
Day31 to Day90 after transplantation	6	31.6	3	360
Day91 to Day180 after transplantation	8	42.1	0	595
> 180 days after transplantation	11	57.9	9	2799

Table 211 Relative incidence of liver transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation - not accounting for perturbed post-event exposure (Subset 1a)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	60 days after any dose vs. other periods	1.51	0.29	7.81
Time since transplantation	0-30 vs. >180 days	3.70	0.73	18.70
	31-90 vs. >180 days	1.44	0.26	7.84
	91-180 vs. >180 days	0.00	0.00	.

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit

Table 212 Relative incidence of liver transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and conditioned to previous rejections (Subset 1a)

No records exist in this table

Table 213 Liver transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix and the time since transplantation - Subjects without previous rejections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	11	100.0	15	4356
Data after censoring according to transplantations	11	100.0	15	3668
Data after censoring according to second rejection	11	100.0	11	3377
Subjects with at least one exposure of interest (Pandemrix, transplantation)	11	100.0	11	3377
Pandemrix - Control period before first dose	10	90.9	7	1681
Pandemrix - Risk period after dose 1	6	54.5	2	276
Pandemrix - Control period after dose 1	5	45.5	2	1147
Pandemrix - Risk period after dose 2	1	9.1	0	61
Pandemrix - Control period after dose 2	1	9.1	0	212
Pandemrix - Pooled risk periods	6	54.5	2	337
Pandemrix - Pooled control periods	11	100.0	9	3040
Day0 to Day30 after transplantation	6	54.5	4	174
Day31 to Day90 after transplantation	6	54.5	1	300
Day91 to Day180 after transplantation	5	45.5	0	398
> 180 days after transplantation	9	81.8	6	2505

Table 214 Relative incidence of liver transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation - Subjects without previous rejections (Subset 1a)

No records exist in this table

Table 215 Liver transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and previous rejection - Subjects with previous rejections (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	1	100.0	1	396
Data after censoring according to transplantations	1	100.0	1	260
Data after censoring according to second rejection	1	100.0	1	260
Subjects with at least one exposure of interest (Pandemrix, Previous rejection, transplantation)	1	100.0	1	260
Pandemrix - Control period before first dose	1	100.0	0	99
Pandemrix - Risk period after dose 1	1	100.0	0	61
Pandemrix - Control period after dose 1	1	100.0	1	100
Pandemrix - Pooled risk periods	1	100.0	0	61
Pandemrix - Pooled control periods	1	100.0	1	199
Day91 to Day180 after transplantation	1	100.0	0	89
> 180 days after transplantation	1	100.0	1	171
Day0 to Day180 after Previous rejection	1	100.0	0	83
> 180 days after Previous rejection	1	100.0	1	177

Table 216 Relative incidence of liver transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and previous rejection - Subjects with previous rejections (Subset 1a)

No records exist in this table

Table 217 Lung transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix and the time since transplantation (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	5	100.0	6	1904
Data after censoring according to transplantations	5	100.0	6	1670
Data after censoring according to second rejection	5	100.0	5	1558
Subjects with at least one exposure of interest (Pandemrix, transplantation)	4	80.0	4	1238
Pandemrix - Control period before first dose	4	80.0	2	345
Pandemrix - Risk period after dose 1	3	60.0	0	102
Pandemrix - Control period after dose 1	1	20.0	0	260
Pandemrix - Risk period after dose 2	2	40.0	0	122
Pandemrix - Control period after dose 2	2	40.0	2	409
Pandemrix - Pooled risk periods	3	60.0	0	224
Pandemrix - Pooled control periods	4	80.0	4	1014
Day0 to Day30 after transplantation	2	40.0	0	41
Day31 to Day90 after transplantation	2	40.0	1	120
Day91 to Day180 after transplantation	2	40.0	0	161
> 180 days after transplantation	3	60.0	3	916

Table 218 Pancreas transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix and the time since transplantation (Subset 1a)

	Subjects			
	N	%	Rejections	Person*days
Subset 1a	1	100.0	1	208
Data after censoring according to transplantations	1	100.0	1	208
Data after censoring according to second rejection	1	100.0	1	208
Subjects with at least one exposure of interest (Pandemrix, transplantation)	1	100.0	1	208
Pandemrix - Control period before first dose	1	100.0	1	57
Pandemrix - Risk period after dose 1	1	100.0	0	61
Pandemrix - Control period after dose 1	1	100.0	0	90
Pandemrix - Pooled risk periods	1	100.0	0	61
Pandemrix - Pooled control periods	1	100.0	1	147
Day91 to Day180 after transplantation	1	100.0	0	15
> 180 days after transplantation	1	100.0	1	193

Table 219 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix and the time since transplantation (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	67	100.0	95	25687
Data after censoring according to transplantations	67	100.0	95	22452
Data after censoring according to second rejection	67	100.0	67	20095
Subjects with at least one exposure of interest (Pandemrix, transplantation)	39	58.2	39	10661
Pandemrix - Control period before first dose	39	58.2	18	3937
Pandemrix - Risk period after dose 1	26	38.8	4	1298
Pandemrix - Control period after dose 1	18	26.9	11	3451
Pandemrix - Risk period after dose 2	8	11.9	1	488
Pandemrix - Control period after dose 2	8	11.9	5	1487
Pandemrix - Pooled risk periods	26	38.8	5	1786
Pandemrix - Pooled control periods	39	58.2	34	8875
Day0 to Day30 after transplantation	16	23.9	6	460
Day31 to Day90 after transplantation	16	23.9	5	779
Day91 to Day180 after transplantation	16	23.9	2	1236
> 180 days after transplantation	32	47.8	26	8186

Table 220 Relative incidence of SOT rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation (Subset 1b)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	60 days after any dose vs. other periods	0.64	0.26	1.58
Time since transplantation	0-30 vs. >180 days	2.13	0.37	12.41
	31-90 vs. >180 days	1.68	0.38	7.45
	91-180 vs. >180 days	0.45	0.05	4.07

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 221 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and seasonal vaccination (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	67	100.0	95	25687
Data after censoring according to transplantations	67	100.0	95	22452
Data after censoring according to second rejection	67	100.0	67	20095
Subjects with at least one exposure of interest (Pandemrix, Seasonal vaccine, transplantation)	49	73.1	49	13868
Pandemrix - Control period before first dose	49	73.1	28	7144
Pandemrix - Risk period after dose 1	26	38.8	4	1298
Pandemrix - Control period after dose 1	18	26.9	11	3451
Pandemrix - Risk period after dose 2	8	11.9	1	488
Pandemrix - Control period after dose 2	8	11.9	5	1487
Pandemrix - Pooled risk periods	26	38.8	5	1786
Pandemrix - Pooled control periods	49	73.1	44	12082
Day0 to Day30 after transplantation	16	23.9	6	460
Day31 to Day90 after transplantation	16	23.9	5	779
Day91 to Day180 after transplantation	16	23.9	2	1236
> 180 days after transplantation	42	62.7	36	11393
Day0 to Day30 after Seasonal vaccine	30	44.8	1	1003
> 30 days after Seasonal vaccine	49	73.1	48	12865

Table 222 Relative incidence of SOT rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and seasonal vaccination (Subset 1b)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	60 days after any dose vs. other periods	0.66	0.27	1.61
Time since transplantation	0-30 vs. >180 days	2.17	0.36	13.14
	31-90 vs. >180 days	1.69	0.36	7.89
	91-180 vs. >180 days	0.47	0.05	4.64
Seasonal influenza vaccination	30 days after vaccination vs. other periods	0.53	0.07	3.89

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 223 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and respiratory infections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	67	100.0	95	25687
Data after censoring according to transplantations	67	100.0	95	22452
Data after censoring according to second rejection	67	100.0	67	20095
Subjects with at least one exposure of interest (Pandemrix, Respiratory infection, transplantation)	40	59.7	40	10995
Pandemrix - Control period before first dose	40	59.7	19	4271
Pandemrix - Risk period after dose 1	26	38.8	4	1298
Pandemrix - Control period after dose 1	18	26.9	11	3451
Pandemrix - Risk period after dose 2	8	11.9	1	488
Pandemrix - Control period after dose 2	8	11.9	5	1487
Pandemrix - Pooled risk periods	26	38.8	5	1786
Pandemrix - Pooled control periods	40	59.7	35	9209
Day0 to Day30 after transplantation	16	23.9	6	460
Day31 to Day90 after transplantation	16	23.9	5	779
Day91 to Day180 after transplantation	16	23.9	2	1236
> 180 days after transplantation	33	49.3	27	8520
Day0 to Day30 after Respiratory infection	3	4.5	0	93
> 30 days after Respiratory infection	40	59.7	40	10902

Table 224 Relative incidence of SOT rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and respiratory infections (Subset 1b)

No records exist in this table

Table 225 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and opportunistic infections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	67	100.0	95	25687
Data after censoring according to transplantations	67	100.0	95	22452
Data after censoring according to second rejection	67	100.0	67	20095
Subjects with at least one exposure of interest (Opportunistic infection, Pandemrix, transplantation)	40	59.7	40	11057
Pandemrix - Control period before first dose	40	59.7	19	4333
Pandemrix - Risk period after dose 1	26	38.8	4	1298
Pandemrix - Control period after dose 1	18	26.9	11	3451
Pandemrix - Risk period after dose 2	8	11.9	1	488
Pandemrix - Control period after dose 2	8	11.9	5	1487
Pandemrix - Pooled risk periods	26	38.8	5	1786
Pandemrix - Pooled control periods	40	59.7	35	9271
Day0 to Day30 after transplantation	16	23.9	6	460
Day31 to Day90 after transplantation	16	23.9	5	779
Day91 to Day180 after transplantation	16	23.9	2	1236
> 180 days after transplantation	33	49.3	27	8582
Day0 to Day30 after Opportunistic infection	4	6.0	0	175
> 30 days after Opportunistic infection	40	59.7	40	10882

Table 226 Relative incidence of SOT rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and opportunistic infections (Subset 1b)

No records exist in this table

Table 227 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and acute bacterial infections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	67	100.0	95	25687
Data after censoring according to transplantations	67	100.0	95	22452
Data after censoring according to second rejection	67	100.0	67	20095
Subjects with at least one exposure of interest (Acute bacterial infection, Pandemrix, transplantation)	39	58.2	39	10661
Pandemrix - Control period before first dose	39	58.2	18	3937
Pandemrix - Risk period after dose 1	26	38.8	4	1298
Pandemrix - Control period after dose 1	18	26.9	11	3451
Pandemrix - Risk period after dose 2	8	11.9	1	488
Pandemrix - Control period after dose 2	8	11.9	5	1487
Pandemrix - Pooled risk periods	26	38.8	5	1786
Pandemrix - Pooled control periods	39	58.2	34	8875
Day0 to Day30 after transplantation	16	23.9	6	460
Day31 to Day90 after transplantation	16	23.9	5	779
Day91 to Day180 after transplantation	16	23.9	2	1236
> 180 days after transplantation	32	47.8	26	8186
> 30 days after Acute bacterial infection	39	58.2	39	10661

Table 228 Relative incidence of SOT rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and acute bacterial infections (Subset 1b)

No records exist in this table

Table 229 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and chronic viral infections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	65	100.0	92	24895
Data after censoring according to transplantations	65	100.0	92	21736
Data after censoring according to second rejection	65	100.0	65	19462
Subjects with at least one exposure of interest (Chronic viral infection, Pandemrix, transplantation)	38	58.5	38	10341
Pandemrix - Control period before first dose	38	58.5	17	3617
Pandemrix - Risk period after dose 1	26	40.0	4	1298
Pandemrix - Control period after dose 1	18	27.7	11	3451
Pandemrix - Risk period after dose 2	8	12.3	1	488
Pandemrix - Control period after dose 2	8	12.3	5	1487
Pandemrix - Pooled risk periods	26	40.0	5	1786
Pandemrix - Pooled control periods	38	58.5	33	8555
Day0 to Day30 after transplantation	15	23.1	5	429
Day31 to Day90 after transplantation	15	23.1	5	719
Day91 to Day180 after transplantation	15	23.1	2	1146
> 180 days after transplantation	31	47.7	26	8047
> 365 days after Chronic viral infection	38	58.5	38	10341

Table 230 Relative incidence of SOT rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and chronic viral infection (Subset 1b)

No records exist in this table

Table 231 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and malignancies/cancers (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	65	100.0	92	24895
Data after censoring according to transplantations	65	100.0	92	21736
Data after censoring according to second rejection	65	100.0	65	19462
Subjects with at least one exposure of interest (Cancer, Pandemrix, transplantation)	39	60.0	39	10737
Pandemrix - Control period before first dose	39	60.0	18	4013
Pandemrix - Risk period after dose 1	26	40.0	4	1298
Pandemrix - Control period after dose 1	18	27.7	11	3451
Pandemrix - Risk period after dose 2	8	12.3	1	488
Pandemrix - Control period after dose 2	8	12.3	5	1487
Pandemrix - Pooled risk periods	26	40.0	5	1786
Pandemrix - Pooled control periods	39	60.0	34	8951
Day0 to Day30 after transplantation	15	23.1	5	429
Day31 to Day90 after transplantation	15	23.1	5	719
Day91 to Day180 after transplantation	15	23.1	2	1146
> 180 days after transplantation	32	49.2	27	8443
Day0 to Day365 after Cancer	2	3.1	2	402
> 365 days after Cancer	39	60.0	37	10335

Table 232 Relative incidence of SOT rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and malignancies/cancers (Subset 1b)

No records exist in this table

Table 233 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and chemotherapy (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	65	100.0	92	24895
Data after censoring according to transplantations	65	100.0	92	21736
Data after censoring according to second rejection	65	100.0	65	19462
Subjects with at least one exposure of interest (Chemotherapy, Pandemrix, transplantation)	41	63.1	41	11529
Pandemrix - Control period before first dose	41	63.1	20	4805
Pandemrix - Risk period after dose 1	26	40.0	4	1298
Pandemrix - Control period after dose 1	18	27.7	11	3451
Pandemrix - Risk period after dose 2	8	12.3	1	488
Pandemrix - Control period after dose 2	8	12.3	5	1487
Pandemrix - Pooled risk periods	26	40.0	5	1786
Pandemrix - Pooled control periods	41	63.1	36	9743
Day0 to Day30 after transplantation	15	23.1	5	429
Day31 to Day90 after transplantation	15	23.1	5	719
Day91 to Day180 after transplantation	15	23.1	2	1146
> 180 days after transplantation	34	52.3	29	9235
Day0 to Day365 after Chemotherapy	5	7.7	2	1336
> 365 days after Chemotherapy	40	61.5	39	10193

Table 234 Relative incidence of SOT rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and chemotherapy (Subset 1b)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	60 days after any dose vs. other periods	0.65	0.26	1.60
Time since transplantation	0-30 vs. >180 days	1.10	0.11	11.48
	31-90 vs. >180 days	1.36	0.21	8.68
	91-180 vs. >180 days	0.40	0.03	5.72
Chemotherapy	365 days after treatment vs. other periods	0.07	0.00	0.99

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 235 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and all covariates (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	65	100.0	92	24895
Data after censoring according to transplantations	65	100.0	92	21736
Data after censoring according to second rejection	65	100.0	65	19462
Subjects with at least one exposure of interest (Acute bacterial infection, Cancer, Chemotherapy, Chronic viral infection, Opportunistic infection, Pandemrix, Respiratory infection, Seasonal vaccine, transplantation)	51	78.5	51	14674
Pandemrix - Control period before first dose	51	78.5	30	7950
Pandemrix - Risk period after dose 1	26	40.0	4	1298
Pandemrix - Control period after dose 1	18	27.7	11	3451
Pandemrix - Risk period after dose 2	8	12.3	1	488
Pandemrix - Control period after dose 2	8	12.3	5	1487
Pandemrix - Pooled risk periods	26	40.0	5	1786
Pandemrix - Pooled control periods	51	78.5	46	12888
Day0 to Day30 after transplantation	15	23.1	5	429
Day31 to Day90 after transplantation	15	23.1	5	719
Day91 to Day180 after transplantation	15	23.1	2	1146
> 180 days after transplantation	44	67.7	39	12380
Day0 to Day30 after Seasonal vaccine	30	46.2	1	1003
> 30 days after Seasonal vaccine	51	78.5	50	13671
Day0 to Day30 after Respiratory infection	3	4.6	0	93
> 30 days after Respiratory infection	51	78.5	51	14581
Day0 to Day30 after Opportunistic infection	4	6.2	0	175
> 30 days after Opportunistic infection	51	78.5	51	14499
> 30 days after Acute bacterial infection	51	78.5	51	14674
> 365 days after Chronic viral infection	51	78.5	51	14674
Day0 to Day365 after Cancer	2	3.1	2	402
> 365 days after Cancer	51	78.5	49	14272
Day0 to Day365 after Chemotherapy	5	7.7	2	1336
> 365 days after Chemotherapy	50	76.9	49	13338

Table 236 Relative incidence of SOT rejection within 60 days after Pandemrix vaccination adjusted for all covariates (Subset 1b)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	60 days after any dose vs. other periods	0.67	0.28	1.63
Time since transplantation	0-30 vs. >180 days	1.12	0.10	12.45
	31-90 vs. >180 days	1.37	0.20	9.44
	91-180 vs. >180 days	0.41	0.03	6.64
Seasonal influenza vaccination	30 days after vaccination vs. other periods	0.53	0.07	4.05
Chemotherapy	365 days after treatment vs. other periods	0.07	0.00	1.05

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 237 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix and the time since transplantation – with subsequent rejections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	67	100.0	95	25687
Data after censoring according to transplantations	67	100.0	95	22452
Subjects with at least one exposure of interest (Pandemrix, transplantation)	39	58.2	55	12084
Pandemrix - Control period before first dose	39	58.2	25	4163
Pandemrix - Risk period after any dose	27	40.3	5	1847
Pandemrix - Control period after any dose	27	40.3	25	6074
Pandemrix - Pooled risk periods	27	40.3	5	1847
Pandemrix - Pooled control periods	39	58.2	50	10237
Day0 to Day30 after transplantation	16	23.9	6	460
Day31 to Day90 after transplantation	16	23.9	7	836
Day91 to Day180 after transplantation	17	25.4	2	1254
> 180 days after transplantation	32	47.8	40	9534

Table 238 Relative incidence of SOT rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation - not accounting for perturbed post-event exposure (Subset 1b)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	60 days after any dose vs. other periods	0.69	0.26	1.81
Time since transplantation	0-30 vs. >180 days	0.89	0.23	3.45
	31-90 vs. >180 days	0.75	0.23	2.47
	91-180 vs. >180 days	0.21	0.04	1.02

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit

Table 239 Relative incidence of SOT rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and conditioned to previous rejections (Subset 1b)

No records exist in this table

Table 240 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix and the time since transplantation - subjects without previous rejections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	33	100.0	46	12680
Data after censoring according to transplantations	33	100.0	46	9913
Data after censoring according to second rejection	33	100.0	33	8908
Subjects with at least one exposure of interest (Pandemrix, transplantation)	33	100.0	33	8908
Pandemrix - Control period before first dose	33	100.0	17	3514
Pandemrix - Risk period after dose 1	20	60.6	2	973
Pandemrix - Control period after dose 1	13	39.4	8	2528
Pandemrix - Risk period after dose 2	7	21.2	1	427
Pandemrix - Control period after dose 2	7	21.2	5	1466
Pandemrix - Pooled risk periods	20	60.6	3	1400
Pandemrix - Pooled control periods	33	100.0	30	7508
Day0 to Day30 after transplantation	14	42.4	6	434
Day31 to Day90 after transplantation	14	42.4	4	659
Day91 to Day180 after transplantation	12	36.4	1	884
> 180 days after transplantation	26	78.8	22	6931

Table 241 Relative incidence of SOT rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation - Subjects without previous rejections (Subset 1b)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	60 days after any dose vs. other periods	0.37	0.12	1.18
Time since transplantation	0-30 vs. >180 days	1.21	0.19	7.81
	31-90 vs. >180 days	1.02	0.24	4.42
	91-180 vs. >180 days	0.08	0.00	1.22

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 242 SOT rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and previous rejection - Subjects with previous rejections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	6	100.0	9	2307
Data after censoring according to transplantations	6	100.0	9	2171
Data after censoring according to second rejection	6	100.0	6	1753
Subjects with at least one exposure of interest (Pandemrix, Previous rejection, transplantation)	6	100.0	6	1753
Pandemrix - Control period before first dose	6	100.0	1	423
Pandemrix - Risk period after dose 1	6	100.0	2	325
Pandemrix - Control period after dose 1	5	83.3	3	923
Pandemrix - Risk period after dose 2	1	16.7	0	61
Pandemrix - Control period after dose 2	1	16.7	0	21
Pandemrix - Pooled risk periods	6	100.0	2	386
Pandemrix - Pooled control periods	6	100.0	4	1367
Day0 to Day30 after transplantation	2	33.3	0	26
Day31 to Day90 after transplantation	2	33.3	1	120
Day91 to Day180 after transplantation	4	66.7	1	352
> 180 days after transplantation	6	100.0	4	1255
Day0 to Day180 after Previous rejection	6	100.0	3	664
> 180 days after Previous rejection	5	83.3	3	1089

Table 243 Relative incidence of SOT rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and previous rejection - Subjects with previous rejections (Subset 1b)

No records exist in this table

Table 244 Heart transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix and the time since transplantation (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	3	100.0	4	1188
Data after censoring according to transplantations	3	100.0	4	1038
Data after censoring according to second rejection	3	100.0	3	938
Subjects with at least one exposure of interest (Pandemrix, transplantation)	2	66.7	2	642
Pandemrix - Control period before first dose	2	66.7	0	91
Pandemrix - Risk period after dose 1	2	66.7	0	122
Pandemrix - Control period after dose 1	2	66.7	2	429
Pandemrix - Pooled risk periods	2	66.7	0	122
Pandemrix - Pooled control periods	2	66.7	2	520
> 180 days after transplantation	2	66.7	2	642

Table 245 Kidney transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix and the time since transplantation (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	34	100.0	51	13007
Data after censoring according to transplantations	34	100.0	51	11071
Data after censoring according to second rejection	34	100.0	34	9626
Subjects with at least one exposure of interest (Pandemrix, transplantation)	26	76.5	26	7003
Pandemrix - Control period before first dose	26	76.5	11	2495
Pandemrix - Risk period after dose 1	18	52.9	3	929
Pandemrix - Control period after dose 1	13	38.2	7	2290
Pandemrix - Risk period after dose 2	5	14.7	1	305
Pandemrix - Control period after dose 2	5	14.7	4	984
Pandemrix - Pooled risk periods	18	52.9	4	1234
Pandemrix - Pooled control periods	26	76.5	22	5769
Day0 to Day30 after transplantation	11	32.4	3	326
Day31 to Day90 after transplantation	11	32.4	3	512
Day91 to Day180 after transplantation	10	29.4	2	768
> 180 days after transplantation	21	61.8	18	5397

Table 246 Relative incidence of kidney transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation (Subset 1b)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	60 days after any dose vs. other periods	0.70	0.28	1.76
Time since transplantation	0-30 vs. >180 days	0.81	0.10	6.33
	31-90 vs. >180 days	1.32	0.22	7.96
	91-180 vs. >180 days	0.58	0.05	7.42

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 247 Kidney transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and seasonal vaccination (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	34	100.0	51	13007
Data after censoring according to transplantations	34	100.0	51	11071
Data after censoring according to second rejection	34	100.0	34	9626
Subjects with at least one exposure of interest (Pandemrix, Seasonal vaccine, transplantation)	28	82.4	28	7790
Pandemrix - Control period before first dose	28	82.4	13	3282
Pandemrix - Risk period after dose 1	18	52.9	3	929
Pandemrix - Control period after dose 1	13	38.2	7	2290
Pandemrix - Risk period after dose 2	5	14.7	1	305
Pandemrix - Control period after dose 2	5	14.7	4	984
Pandemrix - Pooled risk periods	18	52.9	4	1234
Pandemrix - Pooled control periods	28	82.4	24	6556
Day0 to Day30 after transplantation	11	32.4	3	326
Day31 to Day90 after transplantation	11	32.4	3	512
Day91 to Day180 after transplantation	10	29.4	2	768
> 180 days after transplantation	23	67.6	20	6184
Day0 to Day30 after Seasonal vaccine	16	47.1	1	552
> 30 days after Seasonal vaccine	28	82.4	27	7238

Table 248 Relative incidence of kidney transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and seasonal vaccination (Subset 1b)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	60 days after any dose vs. other periods	0.70	0.30	1.67
Time since transplantation	0-30 vs. >180 days	0.81	0.10	6.73
	31-90 vs. >180 days	1.31	0.20	8.75
	91-180 vs. >180 days	0.58	0.04	8.50
Seasonal influenza vaccination	30 days after vaccination vs. other periods	0.92	0.12	7.05

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 249 Kidney transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and respiratory infections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	34	100.0	51	13007
Data after censoring according to transplantations	34	100.0	51	11071
Data after censoring according to second rejection	34	100.0	34	9626
Subjects with at least one exposure of interest (Pandemrix, Respiratory infection, transplantation)	27	79.4	27	7337
Pandemrix - Control period before first dose	27	79.4	12	2829
Pandemrix - Risk period after dose 1	18	52.9	3	929
Pandemrix - Control period after dose 1	13	38.2	7	2290
Pandemrix - Risk period after dose 2	5	14.7	1	305
Pandemrix - Control period after dose 2	5	14.7	4	984
Pandemrix - Pooled risk periods	18	52.9	4	1234
Pandemrix - Pooled control periods	27	79.4	23	6103
Day0 to Day30 after transplantation	11	32.4	3	326
Day31 to Day90 after transplantation	11	32.4	3	512
Day91 to Day180 after transplantation	10	29.4	2	768
> 180 days after transplantation	22	64.7	19	5731
Day0 to Day30 after Respiratory infection	3	8.8	0	93
> 30 days after Respiratory infection	27	79.4	27	7244

Table 250 Relative incidence of kidney transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and respiratory infections (Subset 1b)

No records exist in this table

Table 251 Kidney transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and opportunistic infections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	34	100.0	51	13007
Data after censoring according to transplantations	34	100.0	51	11071
Data after censoring according to second rejection	34	100.0	34	9626
Subjects with at least one exposure of interest (Opportunistic infection, Pandemrix, transplantation)	26	76.5	26	7003
Pandemrix - Control period before first dose	26	76.5	11	2495
Pandemrix - Risk period after dose 1	18	52.9	3	929
Pandemrix - Control period after dose 1	13	38.2	7	2290
Pandemrix - Risk period after dose 2	5	14.7	1	305
Pandemrix - Control period after dose 2	5	14.7	4	984
Pandemrix - Pooled risk periods	18	52.9	4	1234
Pandemrix - Pooled control periods	26	76.5	22	5769
Day0 to Day30 after transplantation	11	32.4	3	326
Day31 to Day90 after transplantation	11	32.4	3	512
Day91 to Day180 after transplantation	10	29.4	2	768
> 180 days after transplantation	21	61.8	18	5397
Day0 to Day30 after Opportunistic infection	2	5.9	0	80
> 30 days after Opportunistic infection	26	76.5	26	6923

Table 252 Relative incidence of kidney transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and opportunistic infections (Subset 1b)

No records exist in this table

Table 253 Kidney transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and acute bacterial infections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	34	100.0	51	13007
Data after censoring according to transplantations	34	100.0	51	11071
Data after censoring according to second rejection	34	100.0	34	9626
Subjects with at least one exposure of interest (Acute bacterial infection, Pandemrix, transplantation)	26	76.5	26	7003
Pandemrix - Control period before first dose	26	76.5	11	2495
Pandemrix - Risk period after dose 1	18	52.9	3	929
Pandemrix - Control period after dose 1	13	38.2	7	2290
Pandemrix - Risk period after dose 2	5	14.7	1	305
Pandemrix - Control period after dose 2	5	14.7	4	984
Pandemrix - Pooled risk periods	18	52.9	4	1234
Pandemrix - Pooled control periods	26	76.5	22	5769
Day0 to Day30 after transplantation	11	32.4	3	326
Day31 to Day90 after transplantation	11	32.4	3	512
Day91 to Day180 after transplantation	10	29.4	2	768
> 180 days after transplantation	21	61.8	18	5397
> 30 days after Acute bacterial infection	26	76.5	26	7003

Table 254 Relative incidence of kidney transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and acute bacterial infections (Subset 1b)

No records exist in this table

Table 255 Kidney transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and chronic viral infections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	34	100.0	51	13007
Data after censoring according to transplantations	34	100.0	51	11071
Data after censoring according to second rejection	34	100.0	34	9626
Subjects with at least one exposure of interest (Chronic viral infection, Pandemrix, transplantation)	26	76.5	26	7003
Pandemrix - Control period before first dose	26	76.5	11	2495
Pandemrix - Risk period after dose 1	18	52.9	3	929
Pandemrix - Control period after dose 1	13	38.2	7	2290
Pandemrix - Risk period after dose 2	5	14.7	1	305
Pandemrix - Control period after dose 2	5	14.7	4	984
Pandemrix - Pooled risk periods	18	52.9	4	1234
Pandemrix - Pooled control periods	26	76.5	22	5769
Day0 to Day30 after transplantation	11	32.4	3	326
Day31 to Day90 after transplantation	11	32.4	3	512
Day91 to Day180 after transplantation	10	29.4	2	768
> 180 days after transplantation	21	61.8	18	5397
> 365 days after Chronic viral infection	26	76.5	26	7003

Table 256 Relative incidence of kidney transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and chronic viral infection (Subset 1b)

No records exist in this table

Table 257 Kidney transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and malignancies/cancers (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	34	100.0	51	13007
Data after censoring according to transplantations	34	100.0	51	11071
Data after censoring according to second rejection	34	100.0	34	9626
Subjects with at least one exposure of interest (Cancer, Pandemrix, transplantation)	26	76.5	26	7003
Pandemrix - Control period before first dose	26	76.5	11	2495
Pandemrix - Risk period after dose 1	18	52.9	3	929
Pandemrix - Control period after dose 1	13	38.2	7	2290
Pandemrix - Risk period after dose 2	5	14.7	1	305
Pandemrix - Control period after dose 2	5	14.7	4	984
Pandemrix - Pooled risk periods	18	52.9	4	1234
Pandemrix - Pooled control periods	26	76.5	22	5769
Day0 to Day30 after transplantation	11	32.4	3	326
Day31 to Day90 after transplantation	11	32.4	3	512
Day91 to Day180 after transplantation	10	29.4	2	768
> 180 days after transplantation	21	61.8	18	5397
> 365 days after Cancer	26	76.5	26	7003

Table 258 Relative incidence of kidney transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and malignancies/cancers (Subset 1b)

No records exist in this table

Table 259 Kidney transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and chemotherapy (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	34	100.0	51	13007
Data after censoring according to transplantations	34	100.0	51	11071
Data after censoring according to second rejection	34	100.0	34	9626
Subjects with at least one exposure of interest (Chemotherapy, Pandemrix, transplantation)	26	76.5	26	7003
Pandemrix - Control period before first dose	26	76.5	11	2495
Pandemrix - Risk period after dose 1	18	52.9	3	929
Pandemrix - Control period after dose 1	13	38.2	7	2290
Pandemrix - Risk period after dose 2	5	14.7	1	305
Pandemrix - Control period after dose 2	5	14.7	4	984
Pandemrix - Pooled risk periods	18	52.9	4	1234
Pandemrix - Pooled control periods	26	76.5	22	5769
Day0 to Day30 after transplantation	11	32.4	3	326
Day31 to Day90 after transplantation	11	32.4	3	512
Day91 to Day180 after transplantation	10	29.4	2	768
> 180 days after transplantation	21	61.8	18	5397
Day0 to Day365 after Chemotherapy	1	2.9	1	295
> 365 days after Chemotherapy	26	76.5	25	6708

Table 260 Relative incidence of kidney transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and chemotherapy (Subset 1b)

No records exist in this table

Table 261 Kidney transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and all covariates (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	34	100.0	51	13007
Data after censoring according to transplantations	34	100.0	51	11071
Data after censoring according to second rejection	34	100.0	34	9626
Subjects with at least one exposure of interest (Acute bacterial infection, Cancer, Chemotherapy, Chronic viral infection, Opportunistic infection, Pandemrix, Respiratory infection, Seasonal vaccine, transplantation)	29	85.3	29	8124
Pandemrix - Control period before first dose	29	85.3	14	3616
Pandemrix - Risk period after dose 1	18	52.9	3	929
Pandemrix - Control period after dose 1	13	38.2	7	2290
Pandemrix - Risk period after dose 2	5	14.7	1	305
Pandemrix - Control period after dose 2	5	14.7	4	984
Pandemrix - Pooled risk periods	18	52.9	4	1234
Pandemrix - Pooled control periods	29	85.3	25	6890
Day0 to Day30 after transplantation	11	32.4	3	326
Day31 to Day90 after transplantation	11	32.4	3	512
Day91 to Day180 after transplantation	10	29.4	2	768
> 180 days after transplantation	24	70.6	21	6518
Day0 to Day30 after Seasonal vaccine	16	47.1	1	552
> 30 days after Seasonal vaccine	29	85.3	28	7572
Day0 to Day30 after Respiratory infection	3	8.8	0	93
> 30 days after Respiratory infection	29	85.3	29	8031
Day0 to Day30 after Opportunistic infection	2	5.9	0	80
> 30 days after Opportunistic infection	29	85.3	29	8044
> 30 days after Acute bacterial infection	29	85.3	29	8124
> 365 days after Chronic viral infection	29	85.3	29	8124
> 365 days after Cancer	29	85.3	29	8124
Day0 to Day365 after Chemotherapy	1	2.9	1	295
> 365 days after Chemotherapy	29	85.3	28	7829

Table 262 Relative incidence of kidney transplant rejection within 60 days after Pandemrix vaccination adjusted for all covariates (Subset 1b)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	60 days after any dose vs. other periods	0.70	0.30	1.67
Time since transplantation	0-30 vs. >180 days	0.81	0.10	6.73
	31-90 vs. >180 days	1.31	0.20	8.75
	91-180 vs. >180 days	0.58	0.04	8.50
Seasonal influenza vaccination	30 days after vaccination vs. other periods	0.92	0.12	7.05

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 263 Kidney transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix and the time since transplantation – with subsequent rejections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	34	100.0	51	13007
Data after censoring according to transplantations	34	100.0	51	11071
Subjects with at least one exposure of interest (Pandemrix, transplantation)	26	76.5	35	7903
Pandemrix - Control period before first dose	26	76.5	13	2579
Pandemrix - Risk period after any dose	18	52.9	4	1234
Pandemrix - Control period after any dose	18	52.9	18	4090
Pandemrix - Pooled risk periods	18	52.9	4	1234
Pandemrix - Pooled control periods	26	76.5	31	6669
Day0 to Day30 after transplantation	11	32.4	3	326
Day31 to Day90 after transplantation	11	32.4	4	536
Day91 to Day180 after transplantation	10	29.4	2	768
> 180 days after transplantation	21	61.8	26	6273

Table 264 Relative incidence of kidney transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation - not accounting for perturbed post-event exposure (Subset 1b)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	60 days after any dose vs. other periods	0.80	0.26	2.43
Time since transplantation	0-30 vs. >180 days	0.39	0.05	3.30
	31-90 vs. >180 days	0.56	0.09	3.41
	91-180 vs. >180 days	0.36	0.06	2.27

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit

Table 265 Relative incidence of kidney transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and conditioned to previous rejections (Subset 1b)

No records exist in this table

Table 266 Relative incidence of kidney transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation - Subjects without previous rejections (Subset 1b)

			95% CI	
Variable	Compared periods	Relative Incidence	LL	UL
Pandemrix	60 days after any dose vs. other periods	0.22	0.06	0.79
Time since transplantation	0-30 vs. >180 days	0.27	0.04	1.80
	31-90 vs. >180 days	0.65	0.15	2.79
	91-180 vs. >180 days	0.04	0.00	1.71

95% CI = 95% Wald confidence interval
LL =lower limit
UL =upper limit
Asymptotic sandwich estimator of covariance matrix

Table 267 Kidney transplant rejection from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and previous rejection - Subjects with previous rejections (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	4	100.0	5	1515
Data after censoring according to transplantations	4	100.0	5	1515
Data after censoring according to second rejection	4	100.0	4	1327
Subjects with at least one exposure of interest (Pandemrix, Previous rejection, transplantation)	4	100.0	4	1327
Pandemrix - Control period before first dose	4	100.0	0	260
Pandemrix - Risk period after dose 1	4	100.0	2	244
Pandemrix - Control period after dose 1	4	100.0	2	823
Pandemrix - Pooled risk periods	4	100.0	2	244
Pandemrix - Pooled control periods	4	100.0	2	1083
Day0 to Day30 after transplantation	1	25.0	0	16
Day31 to Day90 after transplantation	1	25.0	0	60
Day91 to Day180 after transplantation	2	50.0	1	173
> 180 days after transplantation	4	100.0	3	1078
Day0 to Day180 after Previous rejection	4	100.0	2	487
> 180 days after Previous rejection	3	75.0	2	840

Table 268 Relative incidence of kidney transplant rejection within 60 days after Pandemrix vaccination adjusted for the time since transplantation and previous rejection - Subjects with previous rejections (Subset 1b)

No records exist in this table

Table 269 Liver transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix and the time since transplantation (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	11	100.0	14	4356
Data after censoring according to transplantations	11	100.0	14	3359
Data after censoring according to second rejection	11	100.0	11	3241
Subjects with at least one exposure of interest (Pandemrix, transplantation)	8	72.7	8	2385
Pandemrix - Control period before first dose	8	72.7	6	1245
Pandemrix - Risk period after dose 1	4	36.4	1	206
Pandemrix - Control period after dose 1	3	27.3	1	661
Pandemrix - Risk period after dose 2	1	9.1	0	61
Pandemrix - Control period after dose 2	1	9.1	0	212
Pandemrix - Pooled risk periods	4	36.4	1	267
Pandemrix - Pooled control periods	8	72.7	7	2118
Day0 to Day30 after transplantation	4	36.4	3	124
Day31 to Day90 after transplantation	4	36.4	0	207
Day91 to Day180 after transplantation	5	45.5	0	397
> 180 days after transplantation	7	63.6	5	1657

Table 270 Liver transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix the time since transplantation and all covariates (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	10	100.0	13	3960
Data after censoring according to transplantations	10	100.0	13	3039
Data after censoring according to second rejection	10	100.0	10	2921
Subjects with at least one exposure of interest (Acute bacterial infection, Cancer, Chemotherapy, Chronic viral infection, Opportunistic infection, Pandemrix, Respiratory infection, Seasonal vaccine, transplantation)	9	90.0	9	2525
Pandemrix - Control period before first dose	9	90.0	7	1385
Pandemrix - Risk period after dose 1	4	40.0	1	206
Pandemrix - Control period after dose 1	3	30.0	1	661
Pandemrix - Risk period after dose 2	1	10.0	0	61
Pandemrix - Control period after dose 2	1	10.0	0	212
Pandemrix - Pooled risk periods	4	40.0	1	267
Pandemrix - Pooled control periods	9	90.0	8	2258
Day0 to Day30 after transplantation	3	30.0	2	93
Day31 to Day90 after transplantation	3	30.0	0	147
Day91 to Day180 after transplantation	4	40.0	0	307
> 180 days after transplantation	8	80.0	7	1978
Day0 to Day30 after Seasonal vaccine	4	40.0	0	124
> 30 days after Seasonal vaccine	9	90.0	9	2401
> 30 days after Respiratory infection	9	90.0	9	2525
> 30 days after Opportunistic infection	9	90.0	9	2525
> 30 days after Acute bacterial infection	9	90.0	9	2525
> 365 days after Chronic viral infection	9	90.0	9	2525
Day0 to Day365 after Cancer	1	10.0	1	315
> 365 days after Cancer	9	90.0	8	2210
Day0 to Day365 after Chemotherapy	3	30.0	2	750
> 365 days after Chemotherapy	8	80.0	7	1775

Table 271 Lung transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix and the time since transplantation (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	4	100.0	6	1508
Data after censoring according to transplantations	4	100.0	6	1274
Data after censoring according to second rejection	4	100.0	4	1044
Subjects with at least one exposure of interest (Pandemrix, transplantation)	3	75.0	3	724
Pandemrix - Control period before first dose	3	75.0	2	270
Pandemrix - Risk period after dose 1	2	50.0	0	41
Pandemrix - Risk period after dose 2	2	50.0	0	122
Pandemrix - Control period after dose 2	2	50.0	1	291
Pandemrix - Pooled risk periods	2	50.0	0	163
Pandemrix - Pooled control periods	3	75.0	3	561
Day0 to Day30 after transplantation	2	50.0	0	41
Day31 to Day90 after transplantation	2	50.0	2	120
Day91 to Day180 after transplantation	2	50.0	0	161
> 180 days after transplantation	2	50.0	1	402

Table 272 Pancreas transplant rejections from 01-Oct-2009 to 31-Oct-2010 according to the 60-days risk periods of Pandemrix and the time since transplantation (Subset 1b)

	Subjects			
	N	%	Rejections	Person*days
Subset 1b	1	100.0	1	208
Data after censoring according to transplantations	1	100.0	1	208
Data after censoring according to second rejection	1	100.0	1	208
Subjects with at least one exposure of interest (Pandemrix, transplantation)	1	100.0	1	208
Pandemrix - Control period before first dose	1	100.0	1	57
Pandemrix - Risk period after dose 1	1	100.0	0	61
Pandemrix - Control period after dose 1	1	100.0	0	90
Pandemrix - Pooled risk periods	1	100.0	0	61
Pandemrix - Pooled control periods	1	100.0	1	147
Day91 to Day180 after transplantation	1	100.0	0	15
> 180 days after transplantation	1	100.0	1	193

17. ANNEXES

Annex 1 List of stand-alone documents

Number	Document reference number	Date	Title
1.	116602	13-DEC-2013	Annex 1: List of stand-alone documents
2.	116602	13-DEC-2013	Annex 2: Glossary of Terms
3.	116602	13-DEC-2013	Annex 3: Trademarks
4.	116602	13-DEC-2013	Annex 4: Changes in the conduct of the study
5.	116602	13-DEC-2013	Annex 5: Report sign-off

Annex 2 Glossary of Terms

eTrack:	GSK's tracking tool for clinical/epidemiology trials.
Non-interventional (observational) Human Subject Research:	Studies where medicinal products, should they be administered, are prescribed in normal (routine) medical practice. No medical care or medical/scientific procedures as required in a research protocol are administered to participants except as part of routine medical care.
Post-Authorisation Safety Study (PASS):	A pharmaco-epidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product. This includes all GSK sponsored non-interventional studies and clinical trials conducted anywhere in the world that are in accordance with the terms of the European marketing authorisation and where the investigation of safety is the specific stated objective. Note: The phrase, 'In accordance with the terms of the European marketing authorisation' means that the product is used according to the European label (e.g. within the recommended dose range, the approved formulation, indication etc.).
Self-controlled case-series	Method developed to investigate associations between acute outcomes and transient exposures such as vaccination, using only data on cases, that is, on individuals who have experienced the outcome of interest. Inference is within individuals, and hence fixed covariates effects are implicitly controlled for within a proportional incidence framework.
Targeted Safety Study (TSS)	Studies specifically planned or conducted to examine an actual or hypothetical safety concern in a product marketed anywhere in the world. This includes any GSK sponsored pharmacoepidemiology study or clinical trial conduced anywhere in the world with the aim of identifying or quantifying a safety hazard. Although all clinical trials collect safety information as a matter of routine, only those initiated to examine a specific safety concern are considered a targeted safety study.

Annex 3 Trademarks

Trademarks of the GlaxoSmithKline group of companies	Generic description
Pandemrix®	GSK Biologicals' licensed AS03-adjuvanted H1N1 pandemic influenza vaccine
Arepanrix™	GSK Biologicals' licensed AS03-adjuvanted H1N1 pandemic influenza vaccine

Trademarks not owned by the GlaxoSmithKline group of companies	Generic description
Celvapan® (Baxter)	Baxter's licensed influenza vaccine (H1N1): whole virion, inactivated, prepared in cell culture

Annex 4 Changes in the conduct of the study

Please refer to Section 10.9.5 of the main study report.

Annex 5 Report sign-off

Please refer to the modular appendices to the main study report.

MODULAR APPENDICES

List of modular appendices available for the study report and ICH-specific appendices -Study Information equivalent numbering

Modular appendices	ICH numbering
Protocol and protocol amendments.	16.1.1
List of IECs or IRBs (plus name of committee chair if required by regulatory authority)	16.1.3
Representative written information for patient and sample consent forms.	16.1.3
Signatures of principal or coordinating investigator(s) or sponsor?s responsible medical officer, depending on the regulatory authority?s requirement	16.1.5
Important publications referenced in the report.	16.1.12

Protocol and Protocol Amendments

Clinical Study Protocol
Sponsor:
GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium

eTrack study number and Abbreviated Title	116602 (EPI-FLU H1N1-012 VS UK DB)
ISAC protocol number	12_087RA
Date of protocol	Final: 07 September 2012
Date of protocol amendment 1	Final: 15 July 2013
Title	Risk of solid organ transplant rejection following vaccination with Pandemrix™ in the United Kingdom
Detailed Title	A phase IV, retrospective, observational, self-controlled case series analysis in the United Kingdom Clinical Practice Research Datalink GP Online Database to estimate the risk of solid organ transplant rejection following vaccination with Pandemrix™.

Co-ordinating author
- [redacted], Scientific Writer

Contributing authors
- [redacted] - Lead Epidemiologist, GSK Biologicals
- [redacted] - Epidemiologist, GSK Biologicals
- [redacted] - Project Statistician, GSK Biologicals
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- [redacted] - Senior Manager, Statistician Epidemiology, GSK Biologicals
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- [redacted] - Observational Data Analytics, GSK Biologicals
- [redacted] - Director, Observational Data Analytics, GSK R&D
- [redacted] - Global Study Manager, GSK Biologicals
- [redacted] - Therapeutic Area Head, Vaccine Clinical Safety and Pharmacovigilance (VCSP)

GSK Biologicals' Protocol DS v 14.0

ISAC APPLICATION FORM
PROTOCOLS FOR RESEARCH USING THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

ISAC use only: Protocol Number Date submitted		**IMPORTANT** **If you have any queries, please contact ISAC Secretariat:** ISAC@cprd.com

1. Study Title
Risk of solid organ transplant rejection following vaccination with Pandemrix™ in the United Kingdom.
Detailed title:
A phase IV, retrospective, observational, self-controlled case series analysis in the United Kingdom Clinical Practice Research Datalink GP Online Database to estimate the risk of solid organ transplant rejection following vaccination with Pandemrix™

2. Principal Investigator (full name, job title, organisation & e-mail address for correspondence regarding this protocol)
The Principal Investigator for this protocol is [redacted], PhD, Senior Epidemiologist. E-mail: [redacted] - cell phone [redacted]

3. Affiliation (full address)
Epidemiology Department
GlaxoSmithKline Biologicals, Avenue Fleming, 20 - 1300 Wavre - BELGIUM

4. Protocol's Author (if different from the principal investigator)
[redacted], [redacted], [redacted]

5. Type of Institution (please tick one box below)

Academia	☐	Research Service Provider	☐	Pharmaceutical Industry	X
NHS	☐	Government Departments	☐	Others	☐

6. Financial Sponsor of study

Pharmaceutical Industry *(please specify)*	X GSK	Academia *(please specify)*	☐
Government / NHS *(please specify)*	☐	None	☐
Other *(please specify)*	☐		

7. Data source *(please tick one box below)*

CPRD GOLD

Sponsor has on-line access	X	Purchase of ad hoc dataset	☐
Commissioned study	☐		
Other	☐ *(please specify)*		

8. Has this protocol been peer reviewed by another Committee?

Yes*	☐	No	X

** Please state in your protocol the name of the reviewing Committee(s) and provide an outline of the review process and outcome.*

9. Type of Study *(please tick all the relevant boxes which apply)*

Adverse Drug Reaction/Drug Safety	☐	Drug Use	X	Disease Epidemiology	☐
Drug Effectiveness	☐	Pharmacoeconomic	☐	Other	☐

10. This study is intended for:

Publication in peer reviewed journals	X	Presentation at scientific conference	X
Presentation at company/institutional meetings	X	Other: Study report(s) will be sent to the European Medical Agency (EMA)	

11. Does this protocol also seek access to data held under the CPRD Data Linkage Scheme?

Yes X **No** ☐

12. If you are seeking access to data held under the CPRD Data Linkage Scheme, please select the source(s) of linked data being requested.

X **Hospital Episode Statistics** ☐ **Cancer Registry Data*** ☐ **MINAP**
☐ **ONS Mortality Data** ☐ **Index of Multiple Deprivation/ Townsend Score**
☐ **Mother Baby Link** ☐ **Other: (please specify)**

Please note that applicants seeking access to cancer registry data must provide consent for publication of their study title and study institution on the UK Cancer Registry website. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email kc@cprd.com to discuss this requirement further.

13. If you are seeking access to data held under the CPRD Data Linkage Scheme, have you already discussed your request with a member of the Research team?

Yes X **No*** ☐

Please contact the CPRD Research Team on +44 (20) 3080 6383 or email kc@cprd.com to discuss your requirements before submitting your application.

Please list below the name of the person/s at the CPRD with whom you have discussed your request.
- Rachael Boggon
- Emma Boyle
- Mark Hobbs

14. Does this protocol involve requesting any additional information from GPs?

Yes* X **No** ☐

*** Please indicate what will be required:**
Completion of questionnaires by the GP[Ψ] **Yes** X **No** ☐
Provision of anonymised records (e.g. hospital discharge summaries) **Yes** ☐ **No** X
Other (please describe)

[Ψ] ***Any questionnaire for completion by GPs or other health care professional must be approved by ISAC before circulation for completion.***

15. Does this protocol describe a purely observational study using CPRD data (this may include the review of anonymised free text)?

Yes* X **No**** ☐

Yes: If you will be using data obtained from the CPRD Group, this study does not require separate ethics approval from an NHS Research Ethics Committee.
**** No: You may need to seek separate ethics approval from an NHS Research Ethics Committee for this study. The ISAC will provide advice on whether this may be needed.***

16. Does this study involve linking to patient *identifiable* data from other sources?

Yes ☐ **No** X

17. Does this study require contact with patients in order for them to complete a questionnaire?

Yes ☐ **No** X

N.B. Any questionnaire for completion by patients must be approved by ISAC before circulation for completion.

18. Does this study require contact with patients in order to collect a sample?

Yes* ☐ **No** X

**** Please state what will be collected***

19. Experience/expertise available

Please complete the following questions to indicate the experience/expertise available within the team of researchers actively involved in the proposed research, including analysis of data and interpretation of results

	Previous GPRD/CPRD Studies	Publications using GPRD/CPRD data
None	☐	☐
1-3	☐	☐
> 3	X	X

	Yes	No
Is statistical expertise available within the research team?	X	☐
If yes, please outline level of experience	*Experienced statisticians from GSK Biologicals (>10 years' experience) and from the Observational Database Analysis group at GSK Pharma*	
Is experience of handling large data sets (>1 million records) available within the research team?	X	☐
If yes, please outline level of experience	*GSK has large experience in handling large datasets; in this study, analyses will be restricted to a well-characterised population of <500 subjects*	
Is UK primary care experience available within the research team?	X	☐
If yes, please outline level of experience	*Recent experience from a Post-Authorization Safety Study (PASS) of GSK Biologicals' Pandemic Influenza vaccine in the UK, involving primary data collection; extensive experience using GPRD/CPRD GOLD data in the Observational Database Analysis group at GSK Pharma*	

20. References relating to your study

Please list up to 3 references (most relevant) relating to your proposed study.

- Avery RK (2012) Influenza vaccines in the setting of solid-organ transplantation: are they safe? *Curr Opin Infect Dis* **25**: 464-468
- Cordero E, Manuel O (2012) Influenza vaccination in solid-organ transplant recipients. *Curr Opin Organ Transplant* **17**: 601-608
- Nazareth I, Tavares F, Rosillon D, Haguinet F, Bauchau V (2013) Safety of AS03-adjuvanted split-virion H1N1 (2009) pandemic influenza vaccine: a prospective cohort study. *BMJ Open* **3**: 1-13

21. List of all investigators/collaborators (*please list the names, affiliations and e-mail addresses* of all collaborators*, other than the principal investigator)

Main contributing authors:

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- [redacted] (1a), Epidemiologist - [redacted]
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1.GlaxoSmithKline Biologicals, Central Epidemiology (a), GlaxoSmithKline, Worldwide Epidemiology, Observational Data Analytics (b), GlaxoSmithKline Biologicals Clinical Safety and Pharmacovigilance (BCSP)

Please note that your ISAC application form and protocol **must be copied to all e-mail addresses listed above at the time of submission of your application to the ISAC mailbox. Failure to do so will result in delays in the processing of your application.*

PROTOCOL CONTENT CHECKLIST

In order to help ensure that protocols submitted for review contain adequate information for protocol evaluation, ISAC have produced instructions on the content of protocols for research using CPRD data. These instructions are available on the CPRD website (www.cprd.com/ISAC). All protocols using CPRD data which are submitted for review by ISAC must contain information on the areas detailed in the instructions. IF you do not feel that a specific area required by ISAC is relevant for your protocol, you will need to justify this decision to ISAC.

Applicants must complete the checklist below to confirm that the protocol being submitted includes all the areas required by ISAC, or to provide justification where a required area is not considered to be relevant for a specific protocol. Protocols will not be circulated to ISAC for review until the checklist has been completed by the applicant.

Please note, your protocol will be returned to you if you do not complete this checklist, or if you answer 'no' and fail to include justification for the omission of any required area.

	Included in protocol?		
Required area	**Yes**	**No**	**If no, reason for omission**
Lay Summary (max.200 words)	**X**	☐	
Background	**X**	☐	
Objective, specific aims and rationale	**X**	☐	
Study Type ***Descriptive*** ***Hypothesis Generating*** ***Hypothesis Testing***	 ☐ ☐ **X**	 **X** **X**	
Study Design	**X**	☐	
Sample size/power calculation (Please provide justification of sample size in the protocol)	**X**	☐	
Study population (including estimate of expected number of relevant patients in the CPRD)	**X**	☐	
Selection of comparison group(s) or controls	☐	**X**	Not applicable (self-controlled case series)
Exposures, outcomes and covariates ***Exposures are clearly described*** ***Outcomes are clearly described***	**X** **X** **X**	☐ ☐ ☐	
Data/ Statistical Analysis Plan ***There is plan for addressing confounding*** ***There is a plan for addressing missing data***	**X** **X** **X**	☐ ☐ ☐	
Patient/ user group involvement [†]	☐	**X**	No patient or user group could be involved for this specific topic. GSK will report the study results to EMA
Limitations of the study design, data sources and analytic methods	**X**	☐	
Plans for disseminating and communicating study results	**X**	☐	

[†] ***It is expected that many studies will benefit from the involvement of patient or user groups in their planning and refinement, and/or in the interpretation of the results and plans for further work. This is particularly, but not exclusively true of studies with interests in the impact on quality of life. Please indicate whether or not you intend to engage patients in any of the ways mentioned above.***

Voluntary registration of ISAC approved studies:

Epidemiological studies are increasingly being included in registries of research around the world, including those primarily set up for clinical trials. To increase awareness amongst researchers of ongoing research, ISAC encourages voluntary registration of epidemiological research conducted using MHRA databases. This will not replace information on ISAC approved protocols that may be published in its summary minutes or annual report. It is for the applicant to determine the most appropriate registry for their study. Please inform the ISAC secretariat that you have registered a protocol and provide the location.

Risk of solid organ transplant rejection following vaccination with Pandemrix™ in the United Kingdom

Detailed title:

A phase IV, retrospective, observational, self-controlled case series analysis in the United Kingdom Clinical Practice Research Datalink GP Online Database to estimate the risk of solid organ transplant rejection following vaccination with Pandemrix™.

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Other contributing authors: [redacted], PhD[2], [redacted][1a], [redacted] PhD[1b], [redacted][1c], [redacted], PhD , [redacted], MD[1c].

1. GlaxoSmithKline Biologicals, Central Epidemiology (a), GlaxoSmithKline , Worldwide Epidemiology, Observational Data Analytics (b), GlaxoSmithKline Biologicals Clinical Safety and Pharmacovigilance (c).
2. [redacted].

Lay Summary: During the 2009 H1N1 influenza pandemic, mass vaccination with GlaxoSmithKline (GSK)'s inactivated adjuvanted (AS03) A/H1N1 pandemic influenza vaccines Pandemrix™ and Arepanrix™ was initiated in 47 countries, with large coverage and/or single use in several countries. Between October 2009 and March 2010, more than 30 million doses were administered across the European Union (EU), where Pandemrix™ was the predominant vaccine used. Some cases of solid organ transplant (SOT) rejection following vaccination with both vaccines were spontaneously reported. Published reports also described cases of rejection in kidney and heart transplant recipients, while other studies on the safety of pandemic vaccines in patients with lung, kidney, liver and heart transplants showed no events of acute rejection. Seasonal influenza vaccination has also been shown to potentially increase the risk of SOT rejection. Considering that transplant recipients are targeted for immunisation with future pandemic vaccines, the European Medicine's Agency (EMA) requested GSK to further explore the rejection signal and propose a retrospective study in the Clinical Practice Research Datalink GP Online Database (CPRD GOLD). A draft protocol including the results of a feasibility analysis was submitted to EMA on 29 March 2012, and endorsed by EMA's Committee for Medicinal Products for Human Use (CHMP) on 21 June 2012. Results of this study will be communicated to EMA.

There are fourteen Appendices to the present protocol: Appendix A: Algorithms and codes for data extraction; Appendix B: GP questionnaire; Appendix C: Feasibility assessment; Appendix D: Examples of Tables; Appendix E: CPRD GOLD transplantation codes; Appendix F: CPRD GOLD transplant rejection codes; Appendix G: ICD-10 transplantation codes in HES; Appendix H: ICD-10 transplant rejection codes in HES; Appendix I: OPCS 4 procedure codes for transplantation; Appendix J: OPCS-4 procedure codes for transplant rejection; Appendix K: Additional codes to further identify unspecified transplanted organs or the organ related to a rejection episode; Appendix L: CPRD GOLD codes for influenza vaccination; Appendix M: CPRD GOLD codes for infections and chronic conditions; Appendix N: CPRD GOLD codes for malignancies/cancers.

Primary objective:

- To assess the risk of SOT rejection (liver, kidney, lung, heart, pancreas) within one month after vaccination with Pandemrix™.

Secondary objective:

- To assess the risk of SOT rejection (liver, kidney, lung, heart, pancreas) within two months after vaccination with Pandemrix™.

Tertiary objectives:

- To assess the risk of SOT rejection (liver, kidney, lung, heart, pancreas) within one month after seasonal influenza vaccination, during influenza seasons 2006/2007, 2007/2008 and 2008/2009.
- To assess the risk of SOT rejection (liver, kidney, lung, heart, pancreas) within two months after seasonal influenza vaccination, during influenza seasons 2006/2007, 2007/2008 and 2008/2009.

Specific aim: The study is a retrospective, observational, self-controlled case-series (SCCS) in the CPRD GOLD, in patients of all ages with a transplant of the heart, lung, kidney, liver or pancreas, vaccinated with Pandemrix™ or a seasonal influenza vaccine, and who experienced a rejection of the transplanted organ. The specific aim is to assess whether the risk of SOT rejection is increased after vaccination with Pandemrix™ (or a seasonal influenza vaccine).

Background and Rationale: During the 2009 H1N1 influenza pandemic, mass vaccination with GSK's inactivated adjuvanted (AS03) A/H1N1 pandemic influenza vaccines Pandemrix™ and Arepanrix™ was initiated in 47 countries worldwide, with large vaccine coverage and/or single use in several countries (e.g., Finland, Sweden, Canada). Between October 2009 and March 2010, more than 30 million doses were administered across the EU, where Pandemrix™ was the predominant vaccine used. According to data from the UK Department of Health based on the ImmForm national survey, Pandemrix™ was used widely and in the majority of target groups in the UK, with less than 0.1% of individuals having received vaccines from other manufacturers [United Kingdom Department of Health, 2009-2010].
After the pandemic, cases of SOT rejection following vaccination with Pandemrix™ and Arepanrix™ were spontaneously reported in the EU and Canada, respectively. Published reports also described cases temporally associated with vaccination, in kidney and heart transplant recipients immunised with a GSK vaccine [Schaffer, 2011] and in one pancreas transplant recipient immunised with a non-GSK adjuvanted vaccine [Vistoli, 2011]. Other studies on the safety of pandemic vaccines (adjuvanted and non-adjuvanted; from GSK and from other manufacturers) in patients with lung, kidney, liver and heart transplants showed no events of acute rejection [Schuurmans, 2011; Duesberg, 2010; Hauser, 2011; Fairhead, 2011a; Fairhead, 2011b; Goldschmidt, 2011; Altamirano-Diaz, 2011; Torii, 2011; Crespo, 2011; Esposito, 2011; Vazquez-Alvarez, 2010]. All studies were descriptive and based on relatively small sample sizes. The majority of published reports simultaneously evaluated antibody responses to the vaccines and safety. There was substantial heterogeneity between study populations with regards to: patient history (including time since transplantation), overall antibody response to the vaccines, selection criteria for vaccination, vaccination coverage, immune-suppressive drug regimen, case definition for rejection, selection criteria

for biopsy, detection methods for anti-HLA antibodies, presence and adequacy of a control population, and information on background rates of observed events.
While data on the safety of pandemic vaccination in transplanted patients during the 2009 H1N1 pandemic remains relatively limited, it has been postulated that seasonal influenza vaccination might increase the risk of SOT rejection. Although generally administered from 3-6 months post-transplantation [Kumar, 2011], once baseline immune-suppression levels are attained, little data is available on the appropriate timing for influenza immunisation following transplantation. On the other hand, seasonal influenza infection in SOT recipients has been associated with higher morbidity and mortality, graft rejection and prolonged viral shedding [Vilchez, 2002; Weinstock, 2003]. Although the efficacy of seasonal (and pandemic) influenza vaccination in SOT recipients remains controversial, influenza vaccination is advised in transplant recipients [KDIGO, 2009]).

Given the complexity of the outcomes under study, the most appropriate design would be a prospective study allowing standardised definitions for both the patient population and the outcomes. However, this design cannot be considered given that pandemic vaccines are currently not used; therefore, a retrospective observational analysis will be conducted. The proposed design is a SCCS analysis of vaccinated cases, as requested by EMA.

Study Type and Study Design: The SCCS relies on the observation of individuals with the outcome of interest (cases) for both a risk period and control period(s). Since the SCCS analysis relies on case data only, these studies can be performed without the challenges associated with comparison group selection and confounding [Farrington, 1995]. An important feature of this design is that it controls implicitly [Whitaker, 2006] for potential confounders which do not vary with time (e.g. socio-economic status, gender). Additionally, fewer cases are usually required, as compared to a case-control design.

In the present study, the SCCS design requires data on transplant rejection events and on cases' history of pandemic and seasonal influenza vaccination. It is derived from a Poisson model by conditioning on the occurrence of rejection.

The overall study period will range from 01 September 2006 through 31 October 2010. This period will be divided as follows:

- Study period to assess the risk of SOT rejection following vaccination with Pandemrix™ (primary and secondary objectives): 01October 2009 to 31 October 2010.
- Study period to assess the risk of SOT rejection following vaccination with a seasonal influenza vaccine (tertiary objective): 01 September 2006 to 31 August 2009.

The risk period in the primary objective will be one month after vaccination, and two months in the secondary objective. The one-month risk period is based on the latency observed in spontaneous cases reported to GSK, and was agreed by the CHMP; it also corresponds to the most common period with higher risk of rejection following other exposures such as acute infection (Expert advice). The control period will correspond to the overall study period, excluding the risk period(s).

Data sources – CPRD GOLD and Hospital Episodes Statistics (HES): The large majority of transplanted patients are followed in hospital settings. General Practitioners (GP)s are informed of rejection events via discharge letters from hospital departments and specialty care, however, it can be expected that a proportion of events are not encoded by the GPs and thus could be identified via the link between the CPRD GOLD and HES.

The HES database contains details of all admissions to National Health System (NHS) hospitals in England; 56% of GP practices in the CPRD GOLD are linked to the HES database. Not all patients in the CPRD GOLD have linked data (e.g. if they live outside England or if their GP has not agreed that their data should be used in this way). As with standard CPRD GOLD patients, HES data are limited to research-standard patients. CPRD GOLD records are linked to the HES using a combination of the patient's NHS number, gender and date of birth.

Study population: Cases will be identified via a stepwise approach (see Appendix A – Algorithms and codes for data extraction):

Identification of cases

The outcome under study is rejection of at least one of the five transplanted organs (lung, kidney, heart, liver and, pancreas) during the study period. There will be no age limitation. Patients must be considered acceptable in the CPRD GOLD.

The steps of identification of the study population are detailed in Appendix A and summarised in **Figure 1**. The study dataset will be built using the most recent release of the CPRD GOLD available to GSK at the time of approval of this protocol.

Inclusion criteria

- Subject defined as acceptable in the CPRD GOLD;
- Subject with at least one solid organ transplant rejection reported in the CPRD GOLD and/or HES during the study periods (01 September 2006 to 31 August 2009; 01 October 2009 to 31 October 2010).

Exclusion criteria

- Subject from HES ("hesid") matched to more than one subject in the CPRD GOLD ("patid").

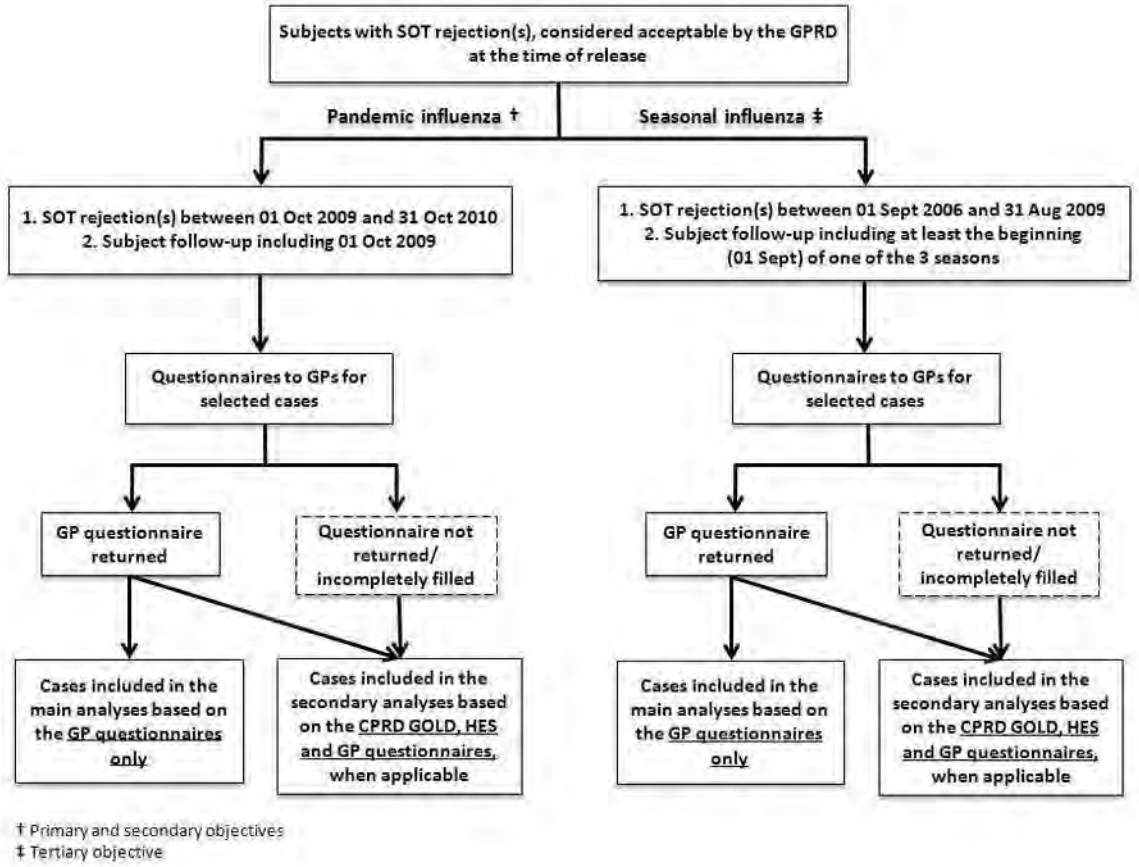
Ascertainment of case status by the GP

For all cases of solid organ transplant rejection, a standard questionnaire will be sent to the GPs via the CPRD GOLD Research Group. Based on the inclusion/exclusion criteria and rules described in the Algorithms (Appendix A), data will be extracted that will allow identifying transplanted patients having experienced at least one rejection in the overall study period (2006-2010). A list of Patient IDs together with the corresponding GP Practice IDs will be provided to the CPRD. The CPRD will in turn send to each identified GP the questionnaire, with guidelines for completion in an attached information sheet. Filled questionnaires returned by the GPs will be anonymised and information sent to the study Principal Investigator (See Appendix B – GP questionnaire).

For a given subject, GPs will be asked:

- To confirm transplantation status and indicate the date of transplantation;
- To provide information on history of rejections including date and type of rejection;
- To report their patient's compliance with treatment before rejection.
- To report information on selected cofactors (e.g., influenza infection, influenza-like illness, opportunistic infections, duration of chemotherapy if applicable);

Figure 1 Identification of the study population



Hypothesis:
Null hypothesis (H0): the incidence rate of solid organ transplant rejection in exposed subjects is the same during the risk period and the control period.
Alternative hypothesis (H1): the incidence rate of solid organ transplant rejection in exposed subjects is different during the risk period and during the control period.

Sample size calculation: sample size was estimated using the following information and assumptions defined based on feasibility data on the incidence of SOT rejection in the former General Practice Research Database (GPRD) in 9,166 transplanted patients (see Appendix C– Feasibility assessment):

- Distribution of transplantation dates (liver, kidney, heart, lung or pancreas) based on GPRD data until 24-Jun-2011;
- Distribution of the first and second doses of Pandemrix™ based on the Post-Authorization Safety Study (PASS) of Pandemrix™ conducted by GSK in the UK general population (N=9,143 subjects) [113585 (EPI-FLU-007 VS UK)] (manuscript submitted);
- Baseline incidence (>90 days post transplantation) of transplant rejection (liver, kidney, heart, lung or pancreas): 13.14 cases per 1,000 patient-years;
- Effect of time since transplantation: true RI between first 31 days (day0-day30) post transplantation and the baseline incidence: 6.22, and between the period from day 31 to day 90 and baseline: 3.09;

- Post-vaccination follow-up period: 181 days. Two risk periods are defined: 31 days (primary objective) and 61 days (secondary objective) after any dose. Control periods: 150 and 120 days, respectively.
- Proportion of subjects having received two doses: 0% or 45%;
- True RI between the risk and control periods: 1, 2, 3, 4 and 5;
- Number of cases: 10, 15, 20, 30 and 40;

For each scenario 1,000 simulations were performed using SAS 9.2. On the basis of the evolution of the incidence of rejection after transplantation, three post-transplantation periods were defined: 0-30, 31-90 and more than 90 days.

Considering that 45% of the transplanted subjects received two doses, and a risk period of 31 days post vaccination (any dose):

- With10 cases, there is 70% power to detect a RI of 5 or higher
- With 20 cases, there is 85% power to detect a RI of 4 or higher
- With 30 cases, there is 80% power to detect a RI of 3 or higher
- With 40 cases, there is 52% power to detect a RI of 2 or higher

Based on these power simulations, no formal analysis will be conducted if the final number of exposed cases is below 10. Nevertheless, identified cases will be described based on their individual record in the CPRD GOLD (e.g. demographics; patient history related to transplantation including rejection; type of organ transplanted; dates of transplantation, H1N1 immunisation, and rejection event following immunisation; immune-suppressive drug regimen; co-morbidities including infections).

Endpoints:

- The endpoint for the primary and secondary objectives is the occurrence of SOT rejection within the period from 01October 2009 to 31 October 2010.
- The endpoint for the tertiary objective is the occurrence of SOT rejection within the period from 01 September 2006 to 31 August 2009.

Data collection: The final study database will consist of data extracted from the CPRD GOLD and HES, and additional data obtained from complementary information provided by the GPs using a standardised questionnaire. Subject data necessary for analysis and reporting will be entered into a validated database or data system and a study-specific dataset will be created. Data management will be performed in accordance with applicable GSK standards. No monitoring will be performed. The study database will be archived by GSK Biologicals' Data Management.

Outcomes definition: The variables will be defined using the algorithms presented in Appendix A. Outcome variables will also be obtained from GP questionnaires. All codes used in this study have been reviewed by a physician.

Statistical methods: Statistical calculations will be performed using the SAS Software version 9.2 or higher. Examples of statistical tables are provided in Appendix D.

1) Subjects' follow-up:

For each subject, the follow-up will be defined separately for each season. The beginning of the follow-up will be 01 October 2009 for the pandemic season, and 01 September of each

season for the other influenza seasons (i.e., 2006/2007, 2007/2008, 2008/2009). The end of follow-up will correspond to whichever of the following dates/events comes first:

- 31 October 2010 for the pandemic study period; 31 August 2007, 2008, or 2009 for the seasonal influenza study periods;
- A new transplantation event as defined in Appendix A;
- Subject's death;
- Last collection date of the GP practice the subject is registered with;
- Transfer out date of the subject: the subject will be included up to the "transfer out date", in order to ensure continuous follow-up during a given season.

2) Subsets of the study population:

Four subsets of cases will be defined for the analyses.

Pandemic influenza study period (01 October 2009 – 31 October 2010):

- Subset 1a. The primary pandemic influenza subset will include subjects:
  - with a follow-up during the pandemic season including 01 October 2009, and
  - with at least one rejection reported in the GP questionnaire, within the subject's follow-up for the pandemic season.
- Subset 1b. The secondary pandemic influenza subset will include:
  - subjects from Subset 1a, and
  - additional subjects from the CPRD GOLD:
    - for whom the GP questionnaire was not returned;
    - with rejection(s) reported in the CPRD GOLD and/or HES between 01 October 2009 and 31 October 2010;
    - with a follow-up during the pandemic season including 01 October 2009.

Seasonal influenza study period (01 September 2006 – 31 August 2009):

- Subset 2a. The primary seasonal influenza subset will include subjects with a follow-up during at least one of the influenza seasons (2006/2007, 2007/2008 or 2008/2009). The subject's follow-up must include:
  - 01 September, and
  - at least one rejection reported in the GP questionnaire in at least one of the 3 influenza seasons.
- Subset 2b. The secondary seasonal influenza subset will include:
  - subjects from Subset 2a, and
  - additional subjects from the CPRD GOLD:
    - for whom the GP questionnaire was not returned;
    - with rejection(s) reported in the CPRD GOLD and/or HES between 01 September 2006 and 31 August 2009;
    - with a follow-up including 01 September in at least one season in which a rejection occurred.

3) Covariates:

The approach used to identify the covariates included in the analyses is detailed in Appendix A.

Pandemrix™ vaccination: A risk period of 31 days (day 0-30) or 61 days (day 0-60) (primary and secondary objectives, respectively) will be associated with each dose. Vaccination information will be extracted from the CPRD GOLD.

Time since transplantation: The period following any transplantation will be divided into four periods corresponding to different risk periods: day 0-30, 31-90, 91-180 and >180. The category >180 days will be the reference in the analyses. If the date of transplantation is missing, a missing category will be defined. All data from the CPRD GOLD, HES and from the GP questionnaire will be used, prioritising information from the GP questionnaire.

Seasonal influenza vaccination: A risk period of 31 days (day0-30) or 61 days (day 0-60) will be associated with each dose. Vaccination information will be extracted from the CPRD GOLD.

Respiratory, opportunistic and acute bacterial infections: A risk period of 31 days (day0-30) will be associated with each occurrence of infection from any data source (CPRD GOLD or GP questionnaire).

Chronic viral infection: A risk period of 366 days (day0-365) will be associated with each occurrence of infection in the CPRD GOLD.

Malignancy/cancer: A risk period of 366 days (day0-365) will be associated with each occurrence of malignancy/cancer in the CPRD GOLD.

Chemotherapy: If duration of chemotherapy is reported in the GP questionnaire, the associated risk period will start at the date of chemotherapy initiation and end 365 days post therapy.

Previous rejection - temporal effect: If one or more rejection episode(s) occur within 180 days before the beginning of the study period of interest (01 October 2009 for the pandemic season, and 01 September of each other influenza seasons), a risk period of 181 days (day0-180) will be associated with the last episode. Day 0 of the risk period will be the date of rejection (as defined in Appendix A).

If the risk periods of several events of the same covariate are overlapping, a combined risk period will span from the start date of the first event to the end date of the last event.

For all covariates except *Time since transplantation* and *previous rejection*, in case of incomplete dates of events reported in the GP questionnaire, two options are considered:

- If the period defined by the incomplete date includes record(s) of the covariate in the CPRD GOLD and/or HES, the corresponding record(s) will be used to determine the associated risk period.
- If no record from CPRD GOLD and/or HES is included in the unknown period, the median of the unknown part (day or month) will be imputed. For instance, --/JUN/2010 changed into 15/JUN/2010, or --/---/2010 changed into 02/JUL/2010.

4) Descriptive Statistics:

Frequency tables will be generated for categorical variables. Mean, median, standard deviation, minimum, maximum will be provided for continuous data such as age.

The following characteristics will be presented:

- Disposition of the study population (Appendix D, Table 2 to Table 5);
- Distribution of subjects and person-time in each influenza season, for each population subset (Appendix D, Table 6);

- Description of influenza vaccine exposure (0, 1, 2 doses) for each season, and for each population subset (Appendix D, Table 7 and Table 8);
- Age and time since transplantation at the beginning of each season, gender, region of GP practice the subject is registered with, number of transplantations during each season, number of rejections within 180 days before the beginning of each season, reasons for end of follow-up (e.g. death, new transplantation, end of study period), and infections/chronic conditions during each season (i.e., respiratory infection, acute bacterial infection, chronic viral infection, opportunistic infection, malignancies/cancers) for each population subset and overall (Appendix D, Table 9 and Table 10).

5) Statistical Analyses:

The association between SOT rejection and influenza vaccination (Pandemrix™ or seasonal influenza vaccination) will be assessed by calculating the relative incidence (RI), which is the ratio of the incidence rate of SOT rejection during the risk period to the incidence rate during the control period, with associated 95% confidence intervals (CI). A single vaccine effect will be estimated for all doses of a given vaccine (Pandemrix™ or seasonal influenza vaccine).

The most important restriction of the SCCS method is the requirement that the occurrence of an event should not change the probability of subsequent exposure [Whitaker 2006]. In the PASS of Pandemrix™ conducted by GSK in the UK, approximately 50% of immuno-compromised individuals received 2 doses [113585 (EPI-FLU-007 VS UK)]; thus, this restriction potentially applies to the present study, as it is likely that the occurrence of a rejection after the first dose of Pandemrix™ would result in the second dose not being administered. Therefore, the case-series analysis for perturbed post-event exposure will be used and the 95% CI will be estimated with the bootstrap method [Farrington, 2009]. The standard SCCS method will be used for sensitivity analyses [Farrington, 1995].

The main limiting assumption of the standard SCCS method is that both the exposure distribution and the observation period must be independent of event times (Farrington et al. 1996). These requirements inhibit use of the case-series method when occurrence of an event alters in some way the subsequent exposure pathway.
In this study, as occurrence of events (transplant rejections) cannot be assumed independent of subsequent exposures (a second dose of Pandemrix™), the recently developed method of "case-series analysis for censored, perturbed, or curtailed post-event exposure (Farrington et al. 2009) will be used to overcome this limitation. The authors developed a model that relaxes the assumption of independence between occurrence of events and subsequent exposures, using a counterfactual modelling approach. The method is based on counterfactuals in which the occurrence of the event precludes future exposures – i.e. a patient experiencing a transplant rejection after the first dose of the vaccine would not receive the second dose. The estimating equations will be established sequentially, starting from the second dose and working back through the first dose, deriving new estimating equations at each stage. The effect of each dose is analysed only in subjects with a rejection event occurring after the considered dose. Where a second dose is administered, the case-series score equations for the first dose are adjusted using an estimator derived from the equations computerised for the second dose. Thus, a set of unbiased estimates is obtained using an iterative procedure.

Primary objective

The risk period will be 31 days (day 0 to day 30) after each dose of Pandemrix™ and the control period will correspond to the subject's follow-up during the season 2009/2010, excluding the risk period.

The primary analysis will be based on Subset 1a (primary pandemic influenza subset). Only rejection events reported in the GP questionnaire will be taken into account. The approach to identify rejection(s) is detailed in Appendix A. No restriction regarding the type of rejection or the immunological mechanism involved will be applied. Only the first rejection after vaccination will be considered. If several rejections occur during the follow-up, the subject will be censored at the second rejection.

Primary analysis for the primary objective:

- Number of rejections and person-time in each risk and control period associated with Pandemrix™ vaccination: control before vaccination, risk after dose1, control after dose1, risk after dose2, control after dose2, etc. (Appendix D, Table 11).
- RI estimates associated with Pandemrix™ vaccination (all doses pooled) adjusted for time since transplantation (Appendix D, Table 12).
- RI estimates associated with Pandemrix™ vaccination adjusted for time since transplantation and seasonal influenza vaccination (Appendix D, Table 13).
- RI estimates associated with Pandemrix™ vaccination adjusted for time since transplantation and for each infection/ chronic condition, malignancy/cancer and chemotherapy in separate models (Appendix D, Table 13).
- RI estimates associated with Pandemrix™ vaccination adjusted for time since transplantation, for seasonal influenza vaccination and for all infections/ chronic conditions, malignancy/cancer and chemotherapy (Appendix D, Table 13).

Sensitivity analyses for the primary objective:

- RI estimates associated with Pandemrix™ vaccination (all doses pooled) adjusted for time since transplantation using the standard SCCS method [Farrington, 1995] (Appendix D, Table 13).
- If more than 5% of subjects from Subset 1a have incomplete rejection dates reported in the GP questionnaire (year and month documented but day missing) and no rejection reported in the CPRD GOLD and/or HES during the month indicated in the GP questionnaire, all analyses detailed above will be conducted with the incomplete dates imputed as follows: --/ MM/YYYY changed into 01/ MM/YYYY, 15/ MM/YYYY or 30 (or 31 or 29 or 28 depending on the specific month)/ MM/YYYY.
- If more than 5% of rejections reported in the GP questionnaire are chronic or of unknown type, these rejections will not be included in the sensitivity analyses.

Secondary analyses for the primary objective:
All the above analyses will be repeated for Subset 1b (secondary pandemic influenza subset)

- with data from the CPRD GOLD/HES only, and
- with data from the CPRD GOLD/HES and from the GP questionnaire, prioritising information from the GP questionnaire for rejections. The approach to identify the rejections for each of these sets is described in Appendix A.

Exploratory analyses for the primary objective:

A previous rejection might influence the risk of a subsequent rejection. Although this effect is partially controlled in the case-series design if it is considered constant during the study period, it could modify the effect of vaccination, or could be time-dependent. Thus, the effect of previous rejection(s) on the risk of subsequent rejection(s) will be investigated through the following sequential analyses:

The modifying effect of a previous rejection will be tested by introducing an interaction term between the fixed effect of a previous rejection and the time-varying effect of vaccination in the model. The fixed effect will be a binary variable: at least one rejection during the 180-day

period before 01 October 2009, or no rejection during this period. The interaction will be tested in the model with adjustment for time since transplantation.

Number of cases allowing, a stratified analysis will be conducted:

- Subjects with no rejection episode before the beginning of the pandemic influenza season, or with rejection episode(s) having occurred >180 days before the beginning of the pandemic influenza season. RI estimate associated with vaccination adjusted for time since transplantation.
- Subjects with at least one rejection episode during the 180-day period prior to the pandemic influenza season. RI estimate associated with vaccination adjusted for time since transplantation and adjusted for the risk period associated with previous rejections.

These exploratory analyses will be based on Subset 1b (secondary pandemic influenza subset). Only subjects with data available during the 180-day period before 01 October 2009 will be considered. Data from the CPRD GOLD/HES and from the GP questionnaire will be used.

Planned analyses will be conducted pooling all organs; additional analyses by organ will be conducted only if 10 rejections are observed for a given organ.

Secondary objective

The same analyses as for the primary objective will be performed, using a risk period of 61 days (Day 0 to Day 60) after any dose of Pandemrix™.

Tertiary objectives

Assuming that rejection events are not independent across the three seasons, data from influenza seasons 2006/2007, 2007/2008 and 2008/2009 will be analysed separately.

For each season, only subjects with follow-up available will be considered for the analyses. The risk periods will span from day 0 to day 30, or from day 0 to day 60, after each seasonal influenza vaccination; the control period will correspond to any period of the follow-up, excluding the risk period.

The primary analysis will be based on Subset 2a (primary seasonal influenza subset). Only rejection events reported in the GP questionnaire will be taken into account. The approach to identify rejection(s) is detailed in Appendix A. No restriction regarding the type of rejection or the immunological mechanism involved will be applied. Only the first rejection after vaccination will be considered. If several rejections occur during the follow-up, the subject will be censored at the second rejection.

Primary analyses for the tertiary objectives:

- Number of cases and person-time in the risk period and control periods (Appendix D, Table 14);
- RI estimates associated with seasonal influenza vaccination adjusted for time since transplantation (Appendix D, Table 15).
- RI estimates associated with seasonal influenza vaccination adjusted for time since transplantation and for each infection/chronic condition, malignancy/cancer and chemotherapy in separate models (Appendix D, Table 15).
- RI estimates associated with seasonal influenza vaccination adjusted for time since transplantation and for all infections/ chronic conditions, malignancy/cancer and chemotherapy (Appendix D, Table 15).

Sensitivity analyses for the tertiary objectives:

- RI estimates associated with the seasonal influenza vaccination exposure adjusted for time since transplantation using the standard SCCS method [Farrington, 1995] (Appendix D, Table 16).
- If more than 5% of subjects from Subset 1a have incomplete rejection dates reported in the GP questionnaire (year and month documented but day missing) and no rejection reported in the CPRD GOLD and/or HES during the month indicated in the GP questionnaire, all analyses detailed above will be conducted with the incomplete dates imputed as follows: --/ MM/YYYY changed into 01/ MM/YYYY, 15/ MM/YYYY or 30 (or 31 or 29 or 28 depending on the specific month)/ MM/YYYY.
- If more than 5% of rejections reported in the GP questionnaire are chronic or of unknown type, these rejections will not be included in the sensitivity analyses.

Secondary analyses for the tertiary objectives:
All the above analyses will be repeated for Subset 2b (secondary seasonal influenza subset)

- with data from the CPRD GOLD/HES only, and
- with data from the CPRD GOLD/HES and from the GP questionnaire, prioritising information from the GP questionnaire for rejections. The approach to identify the rejections for each of these sets is described in Appendix A.

Exploratory analyses for the tertiary objectives:

The modifying effect of a previous rejection will be tested for each season by introducing an interaction term between the fixed effect of a previous rejection and the time-varying effect of seasonal influenza vaccination in the model. The fixed effect will be a binary variable: at least one rejection during the 180-day period before the beginning of the influenza season, or no rejection during this period. The interaction will be tested in the model with adjustment for time since transplantation.

Number of cases allowing, a stratified analysis will be conducted for each influenza season:

- Subjects with no rejection episode before the beginning of the influenza season, or with rejection episode(s) having occurred >180 days before the beginning of the influenza season. RI estimate associated with vaccination adjusted for time since transplantation.
- Subjects with at least one rejection episode during the 180-day period prior to the influenza season. RI estimate associated with vaccination adjusted for time since transplantation and adjusted for the risk period associated with previous rejections.

These analyses will be based on Subset 2b (secondary seasonal influenza subset). Only subjects with data available during the 180-day period before 01 September will be considered for each season. Data from the CPRD GOLD/HES and from the GP questionnaire will be used.

Planned analyses will be conducted pooling all organs; additional analyses by organ will be conducted only if 10 rejections are observed for a given organ.

Statistical models:
The models used in SCCS analyses are based on Poisson regressions (see Farrington, 1995 and Farrington, 2009 for details of the adjustment methods). For all models, the dependent variable will be the number of cases of SOT rejection of all organs and, when applicable, the number of cases of SOT rejection of each organ separately. All models will include the total person-time during each period as an offset. Each model is described hereafter with the list of independent variables.

Pandemic influenza study period

Model1: Vaccination with Pandemrix™, Time since transplantation

Model2: Model1 with vaccination with a seasonal influenza vaccine

Model3: Model1 with respiratory infection(s)

Model4: Model1 with acute bacterial infection(s)

Model5: Model1 with opportunistic infection(s)

Model6: Model1 with chronic viral infection(s)

Model7: Model1 with malignancy(ies)/cancer(s), chemotherapy

Model8: Model2 with respiratory infection(s), acute bacterial infection(s), opportunistic infection(s), chronic viral infection(s), malignancy(ies)/cancer(s), chemotherapy.

Model9: Model1 with interaction between vaccination with Pandemrix™ and fixed effect of previous rejection(s)

Model10: Model1 with temporal effect of previous rejection(s)

Seasonal influenza study period

Model11: Vaccination with a seasonal influenza vaccine, Time since transplantation

Model12: Model11 with respiratory infection(s)

Model13: Model11 with acute bacterial infection(s)

Model14: Model11 with opportunistic infection(s)

Model15: Model11 with chronic viral infection(s)

Model16: Model11 with malignancy(ies)/cancer(s), chemotherapy

Model17: Model11 with respiratory infection(s), acute bacterial infection(s), opportunistic infection(s), chronic viral infection(s) and malignancy(ies)/cancer(s), chemotherapy.

Model18: Model11 with interaction between vaccination with seasonal influenza vaccine and fixed effect of previous rejection(s)

Model19: Model1 with temporal effect of previous rejection(s)

Patient or user group involvement: This study is set up to comply with an EMA commitment. It concerns the analysis of already collected events recorded in a database and occurring in all age subjects of both sexes. No patient or user group could be involved for this specific topic. GSK will report the study results to EMA and will publish the results (see last section of this document).

Study limitations:

Advantages of the study design

- The CPRD GOLD is a large dataset with good representativeness of GPs throughout the UK; age-gender composition of registered individuals is very similar to that of the UK general population.
- The primary health care system in the UK covers a comprehensive population, and the patient population captured in the CPRD GOLD is broadly representative of the demographic breakdown of the UK population.

- During the 2009 pandemic vaccination campaign, immunisation was administered by GPs; therefore, vaccine uptake in the CPRD GOLD accurately represents uptake in the UK, and individual vaccination data is expected to be accurate and comprehensive.
- Pandemic vaccination codes described as both GSK manufactured and with an unbranded / unknown manufacturer will be considered, as recommended by EMA. Both Pandemrix™ and Celvapan™ (Baxter) were used in the UK; however, according to UK data [United Kingdom Department of Health, 2009-2010] and feasibility data from the CPRD GOLD (Appendix C), only 0.1% of individuals received Celvapan™. Thus, the risk of misclassification of exposure is considered marginal and immunisation data will primarily reflect the uptake of Pandemrix™.
- Approximately half of the GP practices in the CPRD GOLD are linked to the HES database, allowing the capture of hospitalisation-related outcomes for linked practices.

Limitations of the study design

- Although GPRD data have been internally and externally validated for various outcomes [Herrett, 2010], it is likely that transplantation status and rejections are not comprehensively and/or properly captured, since these events primarily occur in hospitals and specialty care, and need to be recorded secondarily by the GP.
- A response rate of approximately 80% has been observed in previous studies where GPs were asked to provide individual information based on questionnaires; however, depending on the response rate and the comprehensiveness of the information provided, the number of confirmed cases of SOT rejection for inclusion in the primary analysis could be limited.
- In this database study, there will be an attempt to collect information on lack of compliance to immunosuppressive treatment, co-morbidities, underlying conditions, infections; however, as for any observational study, there may be a number of unmeasured or difficult to assess confounding factors.
- Risk factors for rejection, and magnitude of the risk, vary by organ type [Klein, 2011]; however, given the expected small sample size, it is unlikely that the risk of rejection by organ type can be assessed.
- The risk of rejection might be modified depending on the number of pandemic vaccine doses received; however, the study will probably be underpowered to assess the effect of one vs. two doses.
- Possibly limited statistical power, as highlighted in the feasibility (Appendix C).
- In the analysis of the effect of Pandemrix™, the risk might be confounded by seasonal influenza vaccination; thus, the analysis will be adjusted for a potential effect of seasonal vaccination. However, if both vaccines were administered concomitantly, the SCCS analysis will not allow distinguishing between the effects of the two vaccines.

Study posting, reporting and publications: The results summary will be posted to the GSK Clinical Study Register and other public registers as applicable.

The study results will be reported both internally within GSK and externally to EMA, and a manuscript will be submitted to a peer-reviewed journal for publication.

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GLOSSARY OF TERMS

eTrack:	GSK's tracking tool for clinical/epidemiology trials.
Non-interventional (observational) Human Subject Research:	Studies where medicinal products, should they be administered, are prescribed in normal (routine) medical practice. No medical care or medical/scientific procedures as required in a research protocol are administered to participants except as part of routine medical care.
Post-Authorisation Safety Study (PASS):	A pharmaco-epidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product. This includes all GSK sponsored non-interventional studies and clinical trials conducted anywhere in the world that are in accordance with the terms of the European marketing authorisation and where the investigation of safety is the specific stated objective. Note: The phrase, 'In accordance with the terms of the European marketing authorisation' means that the product is used according to the European label (e.g. within the recommended dose range, the approved formulation, indication etc.).
Self-controlled case-series	Method developed to investigate associations between acute outcomes and transient exposures such as vaccination, using only data on cases, that is, on individuals who have experienced the outcome of interest. Inference is within individuals, and hence fixed covariates effects are implicitly controlled for within a proportional incidence framework.
Targeted Safety Study (TSS)	Studies specifically planned or conducted to examine an actual or hypothetical safety concern in a product marketed anywhere in the world. This includes any GSK sponsored pharmacoepidemiology study or clinical trial conduced anywhere in the world with the aim of identifying or quantifying a safety hazard. Although all clinical trials collect safety information as a matter of routine, only those initiated to examine a specific safety concern are considered a targeted safety study.

LIST OF ABBREVIATIONS

CI	Confidence Interval
CHMP	Committee for Medicinal Products for Human Use
CPRD GOLD	Clinical Practice Research Database GP Online Datalink
EMA	European Medicine's Agency
EU	European Union
GP	General Practitioner
GPRD	General Practice Research Database
GSK	GlaxoSmithKline
HES	Hospital Episodes Statistics
ICD-10	International Classification of Diseases (10^{th} Edition)
ISAC	Independent Scientific Advisory Committee
NHS	National Health System
PASS	Post-Authorisation Safety Study
RI	Relative Incidence
SCCS	Self-Controlled Case-series
SOT	Solid Organ Transplant
UK	United Kingdom

Appendix A: ALGORITHMS AND CODES FOR DATA EXTRACTION

1. IDENTIFICATION OF THE STUDY POPULATION

1.1. General exclusion criteria on data from CPRD GOLD and HES

In addition to the inclusion/exclusion criteria applied at subject level, the following criteria will be applied to the data of each subject.

Exclusion criteria for data from the CPRD GOLD:

- "Eventdate" (date of medical event in the CPRD GOLD) or "system date" (date of recording in CPRD GOLD) before the "Current Registration Date (CRD)" or after the "Transfer Out Date (TOD)";
- "Eventdate" or "system date" before the "Up To Standard date (UTS)" of the GP practice the subject is registered with and after its "Last Collection Date (LCD)".
- All data with "system date" equal to "eventdate" in datasets "clinical" or "referral"

Exclusion criteria for data from HES:

- Match to the CPRD GOLD: category other than 'Strong match' (see variable 22 below for description);
- "epistart" (start date of episode of care) or "evdate" (date of procedure) before the "start date of HES follow-up" (see variable 20 for description) or after the "end date of HES follow-up" (see variable 21 for description).

1.2. Selection of subjects for whom questionnaires will be sent to GPs for the pandemic influenza study period

1. Selection of all subjects with SOT rejection identifier(s) in the CPRD GOLD ('clinical' or 'referral') or HES ('hes_diagnosis_epi', 'hes_procedures_epi') between 01 October 2009 and 31 October 2010.
2. Subject with a follow-up that includes 01 October 2009.

   ↘ Exclusion of subjects with a follow-up period that does not include 01 October 2009.

The subject's follow-up period will be defined as the overlap between:

- the period between the "current registration date" (CRD) and the "transfer out date" (TOD) or death,

And:

- The period between the "Up To Standard date" (UTS) and the "Last Collection Date" (LCD) of the GP practice the subject is registered with.

1.3. Selection of subjects for whom questionnaires will be sent to GPs for the seasonal influenza study period

1. Selection of all subjects with SOT rejection identifier(s) in the CPRD GOLD ('clinical' or 'referral') or HES ('hes_diagnosis_epi', 'hes_procedures_epi') between 01 September 2006 and 31 August 2009.
2. The subject's follow-up period includes the beginning (01 September) of at least one of the season(s) in which the rejection(s) occurred.

   ↘ Exclusion of subjects with a follow-up period that does not include the beginning (01 September) of any of the season(s) in which the rejection(s) occurred.

2. KEY VARIABLES AND DATA

If the algorithms described below do not allow identifying or separating the events of interest, decisions made by the study team during the creation of the analysis datasets will be documented in the statistical report and in the final study report.

2.1. Subject characteristics

Column name	Field name	Description	CPRD GOLD file	Codelist	Comments
1. Patient Identifier	***patid***	Unique identifier given to a patient in the CPRD GOLD	Patient	-	-
2. Patient Gender	***gender***	Patient's gender	Patient	SEX	-
3. Birth Month	***mob***	Patient's month of birth (for those aged under 16), 0 indicates no month set	Patient	-	
4. Birth Year	***yob***	Patient's year of birth	Patient	-	Value+1800
5. Death Date	***deathdate***	Date of death of patient – derived using a CPRD GOLD algorithm	Patient	dd/mm/yyyy[1]	
6. First Registration Date	***frd***	First registration date: Date the patient first registered with the GP practice. If the patient only has 'temporary' records, the date is the first encounter with the practice; if the patient has 'permanent' records it is the date of the first 'permanent' record (excluding preceding temporary records)	patient	dd/mm/yyyy[1]	-
7. Current Registration Date	***crd***	Date the patient's current period of registration with the practice began (date of the first 'permanent' record after the latest transferred out period). If there are no 'transferred out periods', the date is equal to 'frd'	patient	dd/mm/yyyy[1]	-
8. Registration Gaps	***reggap***	Cumulative number of days missing in the patients registration details	patient	PAT_GAP[2]	-
9. Registration Status	***regstat***	Registration status: status of registration detailing gaps and temporary patients	patient	PAT_STAT[3]	-
10. Transfer Out Date	***tod***	Date the patient transferred out of the practice, if relevant. Empty for patients who have not transferred out	patient	dd/mm/yyyy[1]	

Column name	Field name	Description	CPRD GOLD file	Codelist	Comments
11. Transfer Out Reason	***toreason***	Reason the patient transferred out of the practice. Includes 'Death' as an option	patient	TRA	
12. Acceptable Patient Flag	***accept***	Flag to indicate whether the patient has met certain quality standards: 1 = acceptable, 0 = unacceptable	Practice	Boolean	-
13. Practice Identifier	***pracid***	Unique identifier given to a specific practice in the CPRD	Patient_practice	-	Link to the file patient by the variable patid
14. Start date of UTS follow-up	***start***	Max (uts, crd)	Patient_practice	dd/mm/yyyy[1]	Link to the file patient by the variable patid
15. End date of UTS follow-up	***end***	Min (tod, lcd)	Patient_practice	dd/mm/yyyy[1]	Link to the file patient by the variable patid
16. Up To Standard Date	***uts***	Date at which the practice data is deemed to be of research quality. Derived using a CPRD GOLD algorithm that primarily looks at practice death recording and gaps in the data	practice	dd/mm/yyyy[1]	Link to patient_practice file by variable pracid
17. Last Collection Date	***lcd***	Date of the last collection for the practice	practice	dd/mm/yyyy[1]	Link to patient_practice file by variable pracid
18. Region	***region***	Practice region: Value to indicate where in the UK the practice is based	Practice	Lookup PRG	Link to patient_practice file by variable pracid
19. Patient identifier in HES	***hesid***	Unique identifier for a patient in the HES	Hes_source	-	-
20. Start date of HES follow-up	***HESstart***	Start of valid HES data collection for patient: max (01/04/1997, patient's current registration date (crd), practice UTS date)	Hes_source	dd/mm/yyyy[1]	Link to the file patient by the variable patid

Column name	Field name	Description	CPRD GOLD file	Codelist	Comments
21. End date of HES follow-up	***HESend***	End of valid HES data collection for patient: min (31/10/2009, patient's transfer out date, practice last collection date (lcd))	Hes_source	dd/mm/yyyy[1]	Link to the file patient by the variable patid
22. Matching CPRD-HES	***Match***	Flag indicating strength of matching: 0 = No match (never hospitalised or unable to match identifiers) 1 = Strong match (linked using NHS, DOB, & gender); 2 = Matched on DOB, gender, and postcode; 3 = Weak match	Hes_source	-	Link to the file patient by the variable patid
23. Returned GP questionnaire	***GPreturn***	Flag indicating whether the GP questionnaire was returned: 0 = not returned 1 = returned	-	-	-
24. Complete GP questionnaire	***GPcompl***	Flag indicating whether all dates of rejection reported in the GP questionnaire are complete: Missing = GP questionnaire not returned 0 = at least one rejection episode with incomplete or unknown date 1 = all dates of the rejection episodes are complete	-	-	-

dd/mm/yyyy: Valid dates are in the format DD/MM/YYYY. Missing dates are NULL, and invalid dates are set to 01/01/2500

[2] **PAT_GAP:** Number of days between patient's transferred out date and re-registration date for the patient's 'transferred out periods', regardless of whether the transfer was internal or not.

[3] **PAT_STAT:** Transferred out period is the time between a patient transferring out and re-registering at the same practice. If the patient has transferred out for a period of more than 1 day, and the transfer is not internal, this value is incremented. 0 means continuous registration, 1 means one 'transferred out period', 2 means two periods, etc. If the patient only has 'temporary' records then this value is set to 99.

2.2. Derived data for rejections

2.2.1. Primary analyses: episodes reported in the GP questionnaire

Variables	Information
25. Rejection episode	A number will be attributed to each rejection episode reported in the GP questionnaire, except for episodes reported with a missing date or with the year only. The combination of this number with the subject's "patid" will result in a unique identifier for each rejection episode. Only reported episodes that occurred between 01 September 2006 and 31 October 2010 will be considered to build the analysis dataset. In the primary analyses, only rejection episodes reported in the GP questionnaire will be considered. For episodes reported with incomplete dates (i.e., day missing), the CPRD GOLD and/or HES (if available) will be used to estimate the date of the event. However, episodes with the day missing will be ignored if an episode with a complete date is reported during the same month in the GP questionnaire. Rejection episodes reported in the GP questionnaire with a missing date or with only the year reported will be ignored.
26. Start date of the rejection episode	Complete date from the GP questionnaire or date determined from the CPRD GOLD and/or HES for episodes reported with incomplete dates (i.e., day missing). In the CPRD GOLD, the dates to consider are in the variable "eventdate". In HES, it is the "start date" (variable "epistart") of the "episodes of care" for diagnoses and the variable "evdate" for the procedures. <u>Determination of the day for episodes reported with incomplete dates (day missing):</u> Date of the first of all the following records which occurred during the month documented in the GP questionnaire. Only records for the same organ or with no organ specified will be considered: - Records with a medcode from the list in Appendix F in CPRD GOLD datasets 'clinical' or 'referral'. - Records with an ICD10 code from the list in Appendix H in the HES dataset 'hes_diagnosis_epi'. - Records with an OPCS code from the list in Appendix J in the HES dataset 'hes_procedures_epi'. If no record is reported within the corresponding month, the date will remain incomplete, and the episode will only be considered in the sensitivity analyses.
27. Organ rejected	Organ as reported in the GP questionnaire.

Variables	Information
28. Type of rejection	Type of rejection as reported in the GP questionnaire. Four categories of rejection are considered: hyperacute, acute, chronic and unknown.
29. Immunological mechanism	Immunological mechanism as reported in the GP questionnaire. Three categories of rejection are considered: humoral, cellular and unknown.
30. ***Compliance to immuno-suppressive medication 3 months prior to rejection***	Compliance as reported in the GP questionnaire. Five categories of compliance are considered: no immunosuppressive medication, fully compliant, usually compliant, non-compliant and unknown.

2.2.2. Secondary analyses: CPRD GOLD/HES data

Variables	Information
31. Rejection episode	A number will be attributed to each rejection episode. The combination of this number with the subject's "patid" will result in a unique identifier for each rejection episode. Only records from the CPRD GOLD and/or HES with dates between 01 September 2006 and 31 October 2010 will be considered. To ensure that none of the rejections included in the analysis have an onset before 01 September 2006, records of a given patient will be systematically screened 30 days before this date. In the CPRD GOLD, the dates to consider are in the variable "eventdate". In HES, it corresponds to the "start date" (variable "epistart") of the "episodes of care" for diagnoses and the variable "evdate" for the procedures. <u>Rejection episodes will be identified via the following steps:</u> • Records will be identified and chronologically ranked as follows: - Records with a medcode from the list in Appendix F in the CPRD GOLD datasets 'clinical' or 'referral'. - Records with an ICD10 code from the list in Appendix H in HES dataset 'hes_diagnosis_epi'. - Records with an OPCS code from the list in Appendix J in HES dataset 'hes_procedures_epi'. • If a record relates to heart and lung as a single code (medcode = 27679 or ICD10 = T863) then the record will be duplicated to have two separate records with the same date for both organs. • The records with no organ specified (i.e. medcode in [11113, 29831, 50226] or ICD10 code in [T868, T869]) will be linked to the organ-specific record closest in time using rejection(s) or transplantation codes (see Appendix E, F, G, H, I and J for identifiers), or additional records listed in Appendix K. If no organ-specific record is mentioned for a given subject, the organ will remain unspecified. • Within each organ-specific list of records, distinct rejection episodes will be separated by periods of at least 30 days free of rejection records. For rejection(s) of the heart, two episodes will be considered as distinct events, even if separated by less than 30 days, if a new transplantation occurs during this time window. See below for transplantations.
32. Start date of the rejection episode	Event date of the first record of each episode as defined above.

Variables	Information
33. Organ rejected	Organ specified in the rejection episode as defined above (see variable 31 for description). If the organ cannot be determined, it will stay unspecified.

2.2.3. Secondary analyses: combination of GP questionnaires and CPRD GOLD-HES data

Variables	Information
34. Rejection episode	A number will be attributed to each rejection episode. The combination of this number with the subject's "patid" will result in a unique identifier for each rejection episode. All data from the CPRD GOLD and/or HES and from the GP questionnaire will be used for to identify the rejection episodes, prioritising information from the GP questionnaire. The rejection episodes reported in the GP questionnaire with a missing date or with only the year reported will be ignored. For each subject, only records with dates between 01 September 2006 and 31 October 2010 will be considered to build the dataset. To ensure that none of the rejections included in the analysis have an onset before 01 September 2006, records of all subject will be systematically screened 30 days before this date in the CPRD GOLD and/or HES. In the CPRD, the dates to consider are in the variable "eventdate". In HES, it is the "start date" (variable "epistart") of the "episodes of care" for the diagnoses and the variable "evdate" for the procedures. <u>Identification steps for each episode, by organ:</u> 1) Creation of a list of all records for rejection from the CPRD GOLD and/or HES ('database records') for each organ: - Records with a medcode from the list in Appendix F in CPRD GOLD datasets 'clinical' or 'referral'. - Records with an ICD10 code from the list in Appendix H in HES dataset 'hes_diagnosis_epi'. - Records with an OPCS code from the list in Appendix J in HES dataset 'hes_procedures_epi'. - If a record relates to heart and lung as a single code (medcode = 27679 or ICD10 = T863) then the record will be duplicated to have two separate records with the same date for both organs. - The records with no organ specified (i.e. medcode in [11113, 29831, 50226] or ICD10 code in [T868, T869]) will be linked to the organ-specific record closest in time using rejection(s) or transplantation

Variables	Information
	codes (see Appendix E, F, G, H, I and J for identifiers), or additional records listed in Appendix K. If no organ-specific record is mentioned for a subject, the organ will remain unspecified. 2) The following rules will be applied to determine whether rejection records - 'database records' and/or episodes reported in the GP questionnaire ('GP episodes') - correspond to distinct episodes: a) 'GP episodes' with a complete date will be considered as distinct episodes. A 'GP episode' with incomplete date (i.e., day missing) will also be considered to be distinct if the month does not include a 'GP episode' with a complete date, and includes at least one 'database record' identified in step 1). In the sensitivity analyses, a date will be imputed for 'GP episodes' with incomplete dates; these episodes will be considered as 'GP episodes' with complete dates. b) 'database records' with the same calendar month as a 'GP episode' having an incomplete date, will be associated with this 'GP episode'. For rejections of the heart, if a new heart transplantation occurs during this calendar month, the 'GP episode' cannot be used because it cannot be determined whether the rejection occurred before or after the new transplantation; the 'database records' in this calendar month will be used using rule d). c) 'database records' not classified in b) and within an interval [date - 30 days, date + 30 days] around one or more 'GP episodes' with a complete date, will be associated with the closest 'GP episode'. For rejections of the heart, if a new heart transplantation occurs in this interval, the date of the new transplantation will define the lower or upper limit of the interval. d) 'database records' not classified in b) or c) will be grouped in strings of records if they are spaced by ≤30 days. A string will constitute a distinct episode if its limits are spaced by >30 days from any 'database record' classified in b) or c). For rejections of the heart, if a new heart transplantation occurs in between the 'database records' of a string, the string will be split into two distinct episodes. The detection of the transplantations is described below.
35. Date of the rejection episode	The date of each distinct rejection episode will be determined as follows: - Date of rejection of the 'GP episode' if the date is complete; - First 'database record' of the calendar month of the 'GP episode' if the date is incomplete; - Date of the first 'database record' for episodes from 'database records' only.

Variables	Information
36. Organ rejected	Organ specified in the rejection episode as defined above in the identification process of the episodes. If the organ cannot be determined, it will stay unspecified.

2.3. Derived data for transplantations

Variables	Information
37. Transplantation event	A number will be attributed to each transplantation. The combination of this number with the subject's "patid" will result in a unique identifier for each transplantation. All data from the CPRD GOLD and/or HES and from the GP questionnaire will be used to identify the transplantations, prioritising information from the GP questionnaire. Only records with dates between 01 January 2005 and 31 October 2010 will be considered to build the dataset: variable "eventdate" in the CPRD GOLD; variable "epistart" (start date of the episode of care) for diagnoses, and variable "evdate" for procedures in HES. <u>Identification steps for each transplantation, by organ:</u> 1) Creation of a list of all records for new transplantation from the CPRD GOLD and/or HES ('database records') for each organ: - Transplantation records with a medcode from the list [22653, 96423, 72092, 66456, 250, 53626, 61073, 4438, 242, 72939, 58529, 69734, 41495, 9384, 64438, 2997, 55151, 11745, 66705, 24361, 98364, 89924, 96133, 70874, 5504, 5911, 54990, 18774, 4405, 32025, 71422, 89445, 100073, 69194, 97157, 99250, 27319, 9026, 31997, 10461, 96578, 93713, 73743, 38011, 10394 (see Appendix E for descriptions)] in the CPRD GOLD datasets 'clinical' or 'referral'. - Records with an OPCS code for transplantation from Appendix I without M08.4 and M17.4 in HES dataset hes_procedures_epi. - If a record relates to heart and lung in a single code (medcode in [250, 53626, 61073] or OPCS code in [K01.1, K01.8, K01.9]), then the record will be duplicated to have two separate records with the same date for both organs. - The records with no organ specified (i.e. medcode in [22653, 96423, 72092, 66456] will be linked to the

Variables	Information
	organ-specific record closest in time, using rejection(s) or transplantation codes (see Appendix E, F, G, H, I and J for identifiers), or additional records listed in Appendix K. Otherwise, the organ will remain unspecified. 2) The following rules will be applied to determine whether transplantation records -'database records' and/or transplantations reported in the GP questionnaire ('GP transplantations') - correspond to distinct transplantations: a) 'GP transplantations' with a complete date will be considered as distinct transplantations. b) 'database records' within an interval [date - 14 days, date + 14 days] around one or more 'GP transplantations' with a complete date, will be associated with the closest 'GP transplantation'. If several OPCS codes for new transplantation (Appendix I without M08.4 and M17.4) are within the interval, only the code closest to the 'GP transplantation' will be associated with the 'GP transplantation'; the other OPCS codes in the interval will be treated as distinct transplantations (as in c). c) Any new OPCS code for new transplantation (Appendix I without M08.4 and M17.4) not classified in b) will identify a distinct transplantation. d) 'database records' not classified in b) or c) will be grouped in strings of records if they are spaced by ≤14 days. A string will constitute a distinct transplantation if its limits are spaced by >14 days from any 'database record' classified in b) or c). 3) 'GP transplantations' with an incomplete date (day or month missing) will be considered to be distinct if there is no 'database record' during the calendar month (if month/year of transplantation documented) or the calendar year (if year only documented).
38. Date of transplantation	The date of each distinct transplantation will be determined as follows: - Date of 'GP transplantation' if the date is complete. - For 'GP transplantations' with an incomplete date (as in 3) above), the date will remain incomplete. - If the transplantation is identified from 'database records' only, and by a procedure code (as in 1) above), the transplantation date will be the date of the procedure. - Date of the first 'database record' for transplantations from 'database records' only, and with no procedure code.

Variables	Information
39. Organ transplanted	Organ as identified in the transplantation 'database record' and/or 'GP transplantation', as defined above (37). If the organ cannot be determined, it will remain unspecified.

2.4. Derived data for infections and chronic conditions

Variables	Information
40. Infection/ chronic condition identifier	Unique identifier for each infection or chronic condition record. The combination of this identifier with the "patid" will uniquely identify each infection/chronic condition. Only records from the CPRD GOLD and/or HES with dates between 01 September 2005 and 31 October 2010 will be considered to build the dataset. Patient records will be systematically screened as far back as September 2005 to ensure that no infection/chronic condition having started before the study period is missed (corresponding to the 365-day risk period for chronic conditions). All events reported in the GP questionnaire and all records with a medcode from the list in Appendix M in the CPRD GOLD datasets 'clinical' or 'referral' will be included and have an identifier attributed.
41. Code	Medcode for events extracted from the CPRD GOLD.
42. Description	Description of the infection or chronic condition. <u>Data from the GP questionnaire</u>: One of the following: - Influenza virus infection (Laboratory confirmed) - Influenza-like illness - Cytomegalovirus (CMV) - Herpes Simplex Virus (HSV type 1 or 2) - Varicella Zoster Virus (VZV) - Chemotherapy <u>Data from the CPRD:</u> Description of the medcode (Appendix M).

Variables	Information
43. Infection/ chronic condition type	Type of infection or chronic condition: - Respiratory infections - Acute bacterial infections - Chronic viral infections - Opportunistic infections - Malignancies/cancers - Chemotherapy <u>Data from the GP questionnaire</u>: • Respiratory infections: Influenza virus infection (Laboratory confirmed), Influenza-like illness • Opportunistic infections: Cytomegalovirus (CMV), Herpes Simplex Virus (HSV type 1 or 2), Varicella Zoster Virus (VZV) • Chemotherapy <u>Data from the CPRD:</u> See Appendix M for identifiers of each type.
44. Date	Date reported in the GP questionnaire or event date (variable "evtdate") for events extracted from the CPRD GOLD. The incomplete dates of events reported in the GP questionnaires will be managed in the analyses as explained in the main body of this protocol.
45. Duration of chemotherapy	Duration of chemotherapy as reported in the GP questionnaire.

2.5. Derived data for influenza vaccinations

Column name/ Variables name	Algorithm
46. Vaccine dose identifier	Unique identifier for each pandemic influenza vaccine dose administered. The combination of this identifier with the "patid" will uniquely identify each dose. Influenza vaccination data will be extracted from the CPRD.

Column name/ Variables name	Algorithm
47. Vaccine type	Pandemic or seasonal influenza vaccine. <u>Pandemic vaccine:</u> Each vaccination dose will be detected as follows: - Medcode in (94301, 95092, 98217, 98306, 98183, 98184, 98203, 98304) (1st, 2nd dose) AND immstype in (71 [PFLUGEN], 78 [PFLUGENO], 72 [PFLUGSK], 73 [PFLUGSKO], Appendix L) AND status=1 (“given“) in *Immunisation file* - Prodcode in (41150, 41168, Appendix L) in *Therapy file.* Vaccinations detected in the *Therapy file* will be considered to be additional vaccinations if the eventdate is not equal to eventdate (+/- 2 weeks) from *Immunisation file*. Only records between 01-Oct-2009 and 30-Apr-2010 will be taken into account. <u>Seasonal vaccine:</u> Each vaccination will be detected as follows: - Medcode in (6, 97941) AND immstype 4 [FLU] AND status=1 (“given“) in *Immunisation file.* - Prodcode in the list from Appendix L in *Therapy file.* Vaccinations retrieved from *Therapy file* will be considered as additional vaccinations if the eventdate is not equal to eventdate (+/- 2 weeks) from *Immunisation file*. Only records between 01-Sep-2006 and 31-Oct-2010 will be taken into account.
48. Vaccination date	Eventdates from records identified as detailed above (see variable 47 for description)

Appendix B: GP QUESTIONNAIRE

Practice ID	Patient ID	Sex	Year of birth

Study to assess the risk of solid organ transplant rejection

Completion guidelines

GlaxoSmithKline Vaccines is conducting an epidemiological observational study to investigate the risk of rejection in patients with solid organ transplants in the United Kingdom, using the UK Clinical Practice Research Datalink (CPRD) GP Online Database.

In order to complement the information extracted from the CPRD, we would be grateful if you could complete the enclosed short questionnaire to help us gather further information on your patient(s).

Please answer by marking only one cross ☒ for each question, unless more than one answer is allowed (these questions are clearly marked). To enable us encoding your answers, when appropriate please hand write information in capital letters in the blank spaces provided.

Except for Question 1, the remaining 4 questions relate to a study period of January 2005 to December 2010. Only patient information related to this specific period should be reported for Questions 2 to 5.

Depending on the number of transplantations (Question 1) or rejection episodes (Question 2) experienced by your patient(s), Question 1 and Question 2 provide the opportunity to report up to ten events.

We thank you in advance for your valued contribution to this study.

Practice ID	Patient ID	Sex	Year of birth

Please tick the relevant box where appropriate:

Q1. Has this patient undergone solid organ transplantation(s) of the following organs: kidney, liver, pancreas, heart, and lung?

☐ No

☐ Yes → Please complete the following table as best as possible

Transplanted organ (tick all that apply)					**Transplantation date (dd/mm/yyyy) ‡**
Kidney	Liver	Heart	Lung	Pancreas	
☐	☐	☐	☐	☐	….. /….. /……
☐	☐	☐	☐	☐	….. /….. /……
☐	☐	☐	☐	☐	….. /….. /……
☐	☐	☐	☐	☐	….. /….. /……
☐	☐	☐	☐	☐	….. /….. /……
☐	☐	☐	☐	☐	….. /….. /……
☐	☐	☐	☐	☐	….. /….. /……
☐	☐	☐	☐	☐	….. /….. /……
☐	☐	☐	☐	☐	….. /….. /……
☐	☐	☐	☐	☐	….. /….. /……

‡ Please complete as best as possible;

- *If day is unknown, please indicate the month and the year*
- *If day and month are unknown, please indicate the year*

Q2. Has this patient experienced any episode(s) of <u>transplant rejection</u> between 1st January 2005 and 31 December 2010?

☐ No

☐ Yes → Please complete the following table as best as possible

Organ rejected (tick all that apply)	**Date (dd/mm/yyyy)**	**Confirmed by biospy**	**Type**	**Immunological mechanism**	**Immuno-suppressive medication compliance <u>3 months prior to rejection‡</u>**
☐ Kidney ☐ Liver ☐ Heart ☐ Lung ☐ Pancreas	….. /….. /……	☐ Yes ☐ No ☐ Unknown	☐ Hyperacute ☐ Acute ☐ Chronic ☐ Unknown	☐ Humoral ☐ Cellular ☐ Unknown	☐ No immunosuppressive medication ☐ Fully compliant ☐ Usually compliant ☐ Non-compliant ☐ Unknown
☐ Kidney ☐ Liver ☐ Heart ☐ Lung ☐ Pancreas	….. /….. /……	☐ Yes ☐ No ☐ Unknown	☐ Hyperacute ☐ Acute ☐ Chronic ☐ Unknown	☐ Humoral ☐ cellular ☐ Unknown	☐ No immunosuppressive medication ☐ Fully compliant ☐ Usually compliant ☐ Non-compliant ☐ Unknown
☐ Kidney ☐ Liver ☐ Heart ☐ Lung ☐ Pancreas	….. /….. /……	☐ Yes ☐ No ☐ Unknown	☐ Hyperacute ☐ Acute ☐ Chronic ☐ Unknown	☐ Humoral ☐ cellular ☐ Unknown	☐ No immunosuppressive medication ☐ Fully compliant ☐ Usually compliant ☐ Non-compliant ☐ Unknown
☐ Kidney ☐ Liver ☐ Heart ☐ Lung ☐ Pancreas	….. /….. /……	☐ Yes ☐ No ☐ Unknown	☐ Hyperacute ☐ Acute ☐ Chronic ☐ Unknown	☐ Humoral ☐ cellular ☐ Unknown	☐ No immunosuppressive medication ☐ Fully compliant ☐ Usually compliant ☐ Non-compliant ☐ Unknown
☐ Kidney ☐ Liver ☐ Heart ☐ Lung ☐ Pancreas	….. /….. /……	☐ Yes ☐ No ☐ Unknown	☐ Hyperacute ☐ Acute ☐ Chronic ☐ Unknown	☐ Humoral ☐ cellular ☐ Unknown	☐ No immunosuppressive medication ☐ Fully compliant ☐ Usually compliant ☐ Non-compliant ☐ Unknown

‡ Please complete this section based on your best <u>estimate</u> of this patient's compliance with medication

Organ rejected (tick all that apply)	**Date (dd/mm/yyyy)**	**Confirmed by biospy**	**Type**	**Immunological mechanism**	**Immuno-suppressive medication compliance <u>3 months prior to rejection ‡</u>**
☐ Kidney ☐ Liver ☐ Heart ☐ Lung ☐ Pancreas	….. /….. /……	☐ Yes ☐ No ☐ Unknown	☐ Hyperacute ☐ Acute ☐ Chronic ☐ Unknown	☐ Humoral ☐ Cellular ☐ Unknown	☐ No immunosuppressive medication ☐ Fully compliant ☐ Usually compliant ☐ Non-compliant ☐ Unknown
☐ Kidney ☐ Liver ☐ Heart ☐ Lung ☐ Pancreas	….. /….. /……	☐ Yes ☐ No ☐ Unknown	☐ Hyperacute ☐ Acute ☐ Chronic ☐ Unknown	☐ Humoral ☐ cellular ☐ Unknown	☐ No immunosuppressive medication ☐ Fully compliant ☐ Usually compliant ☐ Non-compliant ☐ Unknown
☐ Kidney ☐ Liver ☐ Heart ☐ Lung ☐ Pancreas	….. /….. /……	☐ Yes ☐ No ☐ Unknown	☐ Hyperacute ☐ Acute ☐ Chronic ☐ Unknown	☐ Humoral ☐ cellular ☐ Unknown	☐ No immunosuppressive medication ☐ Fully compliant ☐ Usually compliant ☐ Non-compliant ☐ Unknown
☐ Kidney ☐ Liver ☐ Heart ☐ Lung ☐ Pancreas	….. /….. /……	☐ Yes ☐ No ☐ Unknown	☐ Hyperacute ☐ Acute ☐ Chronic ☐ Unknown	☐ Humoral ☐ cellular ☐ Unknown	☐ No immunosuppressive medication ☐ Fully compliant ☐ Usually compliant ☐ Non-compliant ☐ Unknown
☐ Kidney ☐ Liver ☐ Heart ☐ Lung ☐ Pancreas	….. /….. /……	☐ Yes ☐ No ☐ Unknown	☐ Hyperacute ☐ Acute ☐ Chronic ☐ Unknown	☐ Humoral ☐ cellular ☐ Unknown	☐ No immunosuppressive medication ☐ Fully compliant ☐ Usually compliant ☐ Non-compliant ☐ Unknown

‡ Please complete this section based on your best <u>estimate</u> of this patient's compliance with medication

Q3. Has this patient reported any of the following <u>respiratory infections</u> between 1st January 2005 and 31 December 2010, prioritising the most recent records?

(A) - Influenza virus infection (Laboratory confirmed)
(B) - Influenza-like illness

☐ No

☐ Yes → Please complete the following table as best as possible

Type of respiratory infection	**Date of infection (dd/mm/yyyy)**
☐ A ☐ B	….. /….. /……
☐ A ☐ B	….. /….. /……
☐ A ☐ B	….. /….. /……
☐ A ☐ B	….. /….. /……
☐ A ☐ B	….. /….. /……
☐ A ☐ B	….. /….. /……

Q4. Has this patient reported any of the following <u>opportunistic infections</u> between 1st January 2005 and 31 December 2010, prioritising the most recent records?

(A) – Cytomegalovirus (CMV)
(B) – Herpes Simplex Virus (HSV type 1 or 2)
(C) – Varicella Zoster Virus (VZV)

☐ No

☐ Yes → Please complete the following table as best as possible

Type of opportunistic infection		**Date (dd/mm/yyyy)**
☐ A ☐ B ☐ C	☐ Acute ☐ Reactivation	….. /….. /……
☐ A ☐ B ☐ C	☐ Acute ☐ Reactivation	….. /….. /……
☐ A ☐ B ☐ C	☐ Acute ☐ Reactivation	….. /….. /……
☐ A ☐ B ☐ C	☐ Acute ☐ Reactivation	….. /….. /……
☐ A ☐ B ☐ C	☐ Acute ☐ Reactivation	….. /….. /……
☐ A ☐ B ☐ C	☐ Acute ☐ Reactivation	….. /….. /……

Q5. Has this patient received any <u>chemotherapy</u> between 1st January 2005 and 31 December 2010?

☐ No

☐ Unknown

☐ Yes → Please complete the following table as best as possible

Duration of chemotherapy	**Date of chemotherapy initiation (dd/mm/yyyy)**
Duration (months)…… ☐ Unknown duration	….. /….. /……
Duration (months)…… ☐ Unknown duration	….. /….. /……
Duration (months)…… ☐ Unknown duration	….. /….. /……
Duration (months)…… ☐ Unknown duration	….. /….. /……
Duration (months)…… ☐ Unknown duration	….. /….. /……
Duration (months)…… ☐ Unknown duration	….. /….. /……

Please complete this section based on your best <u>estimate</u> of this patient's chemotherapy duration.

Many thanks for your time in completing this questionnaire.
Please now return it in the freepost envelope provided

Appendix C: FEASIBILITY ASSESSMENT

This feasibility assessment was undertaken irrespective of any pre-specified study design, with the main goal of obtaining estimates of the number of transplanted patients and of the number of rejections in the former GPRD and HES.

Feasibility in the GPRD

Search for READ codes relevant to the outcomes under study was performed stepwise:

Transplantation codes:

- Step 1: screening of the GPRD, using specific READ Codes [e.g. search for READ codes of format ZV42*] to identify and list all clinical terms related to solid organ transplantation.
  - READ codes were identified from the specialised BioPortal website (Read Codes, Clinical Terms Version 3) [Bioportal Website].
  - Clinical terms were reviewed by a clinician (GSK UK).
- Step 2: screening of the GPRD using specific keywords (i.e., transplantation, transplant, graft) associated with terms related to the organs of interest (i.e., cardiology, heart, pulmonary, lung, kidney, renal, liver, hepatic, pancreas) to generate a second list of terms potentially related to transplantation.
- Step 3: combination of the two lists and selection of relevant codes by clinical review to build the final list of transplantation codes

Transplant rejection codes:

- Step 4: screening of the GPRD, using specific READ Codes, to identify and list all clinical terms related to transplant rejection that are associated with the transplantation codes identified in Step 3.
- Step 5: screening of the GPRD, using specific keywords (i.e., rejection, complication, failure) associated with terms related to the organs of interest (i.e., cardiology, heart, pulmonary, lung, kidney, renal, liver, hepatic, pancreas) to generate a second list of terms potentially related to transplant rejection.
- Step 6: combination of the two lists and selection of relevant codes by clinical review to build the final list of transplant rejection codes.

The GPRD was explored using the selected transplantation codes, with no restrictions on patient start or end date; however, to be included, a patient had to be acceptable as per GPRD criteria at the date of transplantation and to have a valid date of transplantation.

Each event in the GPRD has an associated system date that represents the date at which the data was entered; the system date does not always correspond to the date at which the GP observed or recorded an event. To establish whether an event was entered subsequently to its occurrence, the following rules were applied:

- Event date equal to system date: the event date is assumed to be invalid (since these events will occur while hospitalised rather than while visiting the GP). Similarly if the event date is unknown or occurs at least one year before the estimated date of birth, then the date is deemed invalid.
- Event date before the patient is registered in the GPRD: the date is considered unreliable (since this prior information was likely to be entered in batch on the same date or close to registration).
- Event date before the date the practice used the latest software: the date is considered unreliable.

- Event date is within the first 3 months of registration in the GPRD: the date is considered unreliable (often there is a time lag before the transferring of information from the prior practice which is then all entered on the same date).

Remaining events were assumed to be valid and having occurred on the recorded event date, which in all instances will differ from the system date for that record.

The search yielded a total of 40,991 notes of transplantation (i.e. any entry related to a transplantation or transplantation-related event or procedure), corresponding to a total of 6,866 transplanted subjects (kidney: 5,051; liver: 896; heart: 561; lung: 158; pancreas: 29 unspecified organ: 171). Of these, 340 (5%) had a date of transplantation identical to the system date and 4,608 (67%) had an unreliable date, resulting in a total of N= 1,918 subjects with a valid transplantation date (28%).
Using the selected rejection codes, 48 patients with a rejection between 01 October 2009 and 31 October 2010 and with follow-up on the GPRD at the date of rejection, were identified; of these, dates appear valid for 33 patients (68.8%).

Feasibility in the HES database

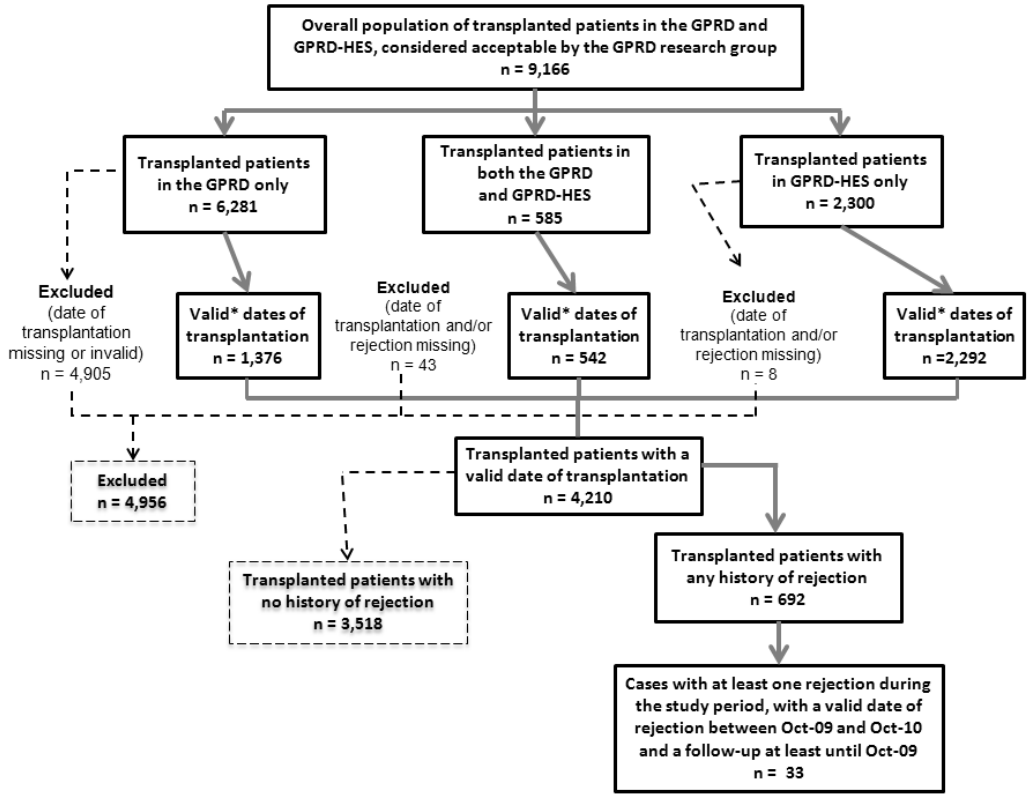
At the time of feasibility assessment, 48% of GP practices in the GPRD were linked to HES.
A search of linked HES records for transplanted patients and rejection events was performed using relevant ICD-10 (International Classification of Diseases, 10th edition) codes to:

- Compare dates between GPRD and HES, to ensure consistency of the outcome.
- Find additional cases of rejection not encoded in the GPRD.

When the exact date of transplantation or rejection was not available in HES, the admission date for the hospitalisation was used.
Restricting the search to transplanted patients, the proportion of patients linked between the GPRD and GPRD-HES is 63%.
Restricting the request to the GPRD-HES database, the search yielded a total of 18,486 notes of transplantation, resulting in a total of 2,300 transplanted subjects (kidney: 525; liver: 121; heart: 207; lung: 103; pancreas: 11; unspecified organ: 1,333). Of these, 8 had a missing date of transplantation, resulting in a total of 2,292 subjects with a valid transplantation date (99.6%).

In conclusion, combining searches in the GPRD and the GPRD-HES resulted in a total of 59,477 notes of transplantation, corresponding to 9,166 transplanted patients, including 4,210 (45.9%) with a valid date of transplantation.

Figure 2 Estimation of the number of transplanted patients and rejection events in the GPRD and HES



Vaccination codes and vaccination coverage in the GPRD:

For pandemic H1N1 vaccination, vaccination events are either described as GSK manufactured or with an unbranded / unknown manufacturer. Based on the data from the ImmForm survey [United Kingdom Department of Health, 2009-2010], immunisation data should primarily reflect the uptake of Pandemrix.

Pandemic and seasonal influenza vaccination codes are described in Appendix L.
A search for records of vaccination with Pandemrix™ in the GPRD indicated a total of 540,927 individuals with at least one note of vaccination. There were 524,708 individuals with a note of vaccination between 1st October 2009 and 30th April 2010 while followed on the GPRD. There were a total of 4,516,021 individuals followed as at 1st October 2009 and 4,474,884 patients followed as at 30th April 2010, giving an estimate of the overall vaccination coverage for Pandemrix in the GPRD of 11.7%.

Among transplanted patients identified in the GPRD, 34.1% were vaccinated with at least one dose of Pandemrix. This rate reaches 55.4%, when the search was limited to transplanted patients with a continuous follow-up during the vaccination period (October 2009 – April 2010).

Table 1 Counts of seasonal and pandemic influenza vaccination

Season	Coverage in the GPRD	Coverage in SOT patients (n=9,166)	Coverage in SOT patients with follow-up after Oct-09 (n=4,372)
2006-2007 Seasonal vaccination	898,652/4,557,707 (19.7%)	2,967 (32.4%)	2,324 (53.2%)
2007-2008 Seasonal vaccination	884,940/4,575,588 (19.3%)	2,871 (31.3%)	2,425 (55.5%)
2008-2009 Seasonal vaccination	896,236/4,560,145 (19.7%)	2,908 (31.7%)	2,629 (60.1%)
2009-2010 Seasonal vaccination	890,282/4,522,478 (19.7%)	2,967 (32.4%)	2,871 (65.7%)
2009/2010 Pandemic vaccination	524,708/4,495,453 (11.7%)	**At least 1 dose** 3,123 (34.1%)	**At least 1 dose** 2,424 (55.4%)
		2 doses 1,054 (11.5%)	**2 doses** 1,054 (24.1%)

Appendix D: EXAMPLES OF TABLES

Table 2 Selection of the study population for the pandemic influenza study period

Title	Total	Percent
Subjects flagged as Acceptable in the CPRD GOLD		-
Subject from HES (”hesid”) matched to only one subject in the CPRD GOLD (“patid”)		
Subjects with SOT rejection identifier(s) in the CPRD GOLD and/or HES between 01-Oct-2009 and 31-Oct-2010		
Subjects having 01 October 2009 included in their follow-up period		
Subjects with GP questionnaire returned		

Note: Each row is a subset from the previous one

Table 3 Selection of the study population for the seasonal influenza study period

Title	Total	Percent
Subjects flagged as Acceptable in the CPRD GOLD		-
Subject from HES (”hesid”) matched to only one subject in the CPRD GOLD (“patid”)		
Subjects with SOT rejection identifier(s) in the CPRD GOLD and/or HES between 01-Sep-2006 and 31-Aug-2009		
Subjects having the beginning (01 September) of at least one of the season(s) in which the rejection(s) occurred included in their follow-up period		
Subjects with GP questionnaire returned		

Note: Each row is a subset from the previous one

Table 4 Number of subjects enrolled into the pandemic influenza part of the study

Title	Total	Percent
Secondary pandemic influenza subset		-
Subjects with no rejection event reported in the GP questionnaire within their individual follow-up in CPRD GOLD		
Primary pandemic influenza subset		

Table 5 Number of subjects enrolled into the seasonal influenza part of the study

Title	Total	Percent
Secondary seasonal influenza subset		
Subjects with no rejection event reported in the GP questionnaire within their complete follow-up periods of any of the seasons 2006/2007, 2007/2008 and 2008/2009.		
Primary seasonal influenza subset		

Table 6 Distribution of subjects and person-time into each influenza study period for each subset

Subset	Influenza season	N	%	Person-years
Primary pandemic influenza subset	2009/2010		-	
Secondary pandemic influenza subset	2009/2010		-	
Primary seasonal influenza subset	2006 - 2009		-	
	2006/2007			
	2007/2008			
	2008/2009			
Secondary seasonal influenza subset	2006 - 2009		-	
	2006/2007			
	2007/2008			
	2008/2009			

N: Number of subjects considered in the influenza season
%: Percentage of subjects considered in the influenza season in the corresponding subset

Table 7 Description of vaccine exposure in the pandemic influenza study period

Subset	Influenza vaccine	Vaccination	N	n	%
Primary pandemic influenza subset	Pandemrix™	Not vaccinated			
		1 dose			
		2 doses			
		> 2 doses			
	Seasonal	Not vaccinated			
		Vaccinated			
Secondary pandemic influenza subset	Pandemrix™	Not vaccinated			
		1 dose			
		2 doses			
		> 2 doses			
	Seasonal	Not vaccinated			
		Vaccinated			

N: Number of subjects in the subset
n/%: Number/Percentage of subjects in each category

Table 8 Description of vaccine exposure in the seasonal influenza study period

Subset	Influenza season	Vaccination	N	n	%
Primary seasonal influenza subset	2006/2007	Not vaccinated			
		Vaccinated			
	2007/2008	Not vaccinated			
		Vaccinated			
	2008/2009	Not vaccinated			
		Vaccinated			
Secondary seasonal influenza subset	2006/2007	Not vaccinated			
		Vaccinated			
	2007/2008	Not vaccinated			
		Vaccinated			
	2008/2009	Not vaccinated			
		Vaccinated			

N: Number of subjects in the considered subset and season
n/%: Number/Percentage of subjects in each category

Table 9 Demographic and baseline characteristics (<pandemic influenza subset>)

		Vaccinated N =		Not Vaccinated N =		Total N =	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Age at 01-Oct-2009 (years)	Mean						
	SD						
	Median						
	Minimum						
	Maximum						
Age group at 01-Oct-2009 (years)	0-17						
	18-44						
	45-60						
	> 60						
Gender	Female						
	Male						
Died between 01-Oct-2009 and 31-Oct-2010	No						
	Yes						
Time since transplantation at 01-Oct-2009 (days)	Not yet*						
	0-30						
	31-90						
	91-180						
	180-365						
	>365						
Organ transplanted before or during the season**	Heart						
	Kidney						
	Liver						
	Lung						
	Pancreas						
	Heart+Lung						
	…						
Number of rejections between 04-Apr-2009 and 01-Oct-2009	None						
	At least one						
	Missing						
Number of transplantation events between 01-Oct-2009 and 31-Oct-2010	0						
	1						
	2						
	…						
Respiratory infection(s) between 31-Aug-2009 and 31-Oct-2010	No						
	Yes						
Acute bacterial infection(s) between 31-Aug-2009 and 31-Oct-2010	No						
	Yes						
Opportunistic infection(s) between 31-Aug-2009 and 31-Oct-2010	No						
	Yes						
Chronic viral infection(s) between 30-Sep-2008 and 31-Oct-2010	No						
	Yes						
Reasons for end of follow-up	End of pandemic study period (31-Oct-2010)						
	New transplantation						

		Vaccinated N =		Not Vaccinated N =		Total N =	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Organ transplanted before or during the season**	Death						
	End of CPRD GOLD follow-up						

*Transplantations could happen after 01-Oct-2009; **Each subject is classified in one category. All combinations are possible

Table 10 Demographic and baseline characteristics of subjects with data for season <2006-2007> (<seasonal influenza subset>)

		Vaccinated N =		Not Vaccinated N =		Total N =	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Age at 01-Sep-<2006> (years)	Mean						
	SD						
	Median						
	Minimum						
	Maximum						
Age group at 01-Sep-<2006> (years)	0-17						
	18-44						
	45-60						
	> 60						
Gender	Female						
	Male						
Died between 01-Sep-<2006> and 31-Aug-<2007>	No						
	Yes						
Time since transplantation at 01-Sep-<2006> (days)	Not yet*						
	0-30						
	31-90						
	91-180						
	>180						
	Missing						
Organ transplanted before or during the season**	Heart						
	Kidney						
	Liver						
	Lung						
	Pancreas						
	Heart+Lung						
	…						
Number of rejections between 05-Mar-<2006> and 01-Sep-<2006>	None						
	At least one						
	Missing						
Number of transplantation events between 01-Sep-<2006> and 31-Aug-<2007>	0						
	1						
	2						
	…						
Respiratory infection(s) between 01-Aug-<2006> and 31-Aug-<2007>	No						
	Yes						
Acute bacterial infection(s) between 01-Sep-<2006> and 31-Aug-	No						
	Yes						

		Vaccinated N =		Not Vaccinated N =		Total N =	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
<2007>							
Opportunistic infection(s) between 01-Sep-<2006> and 31-Aug-<2007>	No						
	Yes						
Chronic viral infection(s) between 01 Sep 2006 and 31-Aug-<2006>	No						
	Yes						
Malignancy/cancer(s) between 01 Sep-Aug-<2006> and 31-Aug-<2007>	No						
	Yes						
Reasons for end of follow-up	End of pandemic study period (31-Oct-2010)						
	New transplantation						
	Death						
	End of CPRD GOLD follow-up						

* Transplantations could happen after 01-Sep-<2006>

** Each subject is classified in one category. All combinations are possible

Table 11 SOT rejections from <01-Oct-2009 to 31-Oct-2010> in the <risk period> and control periods (<pandemic influenza subset>)

Period	Number of cases	Person*years
From <01-Oct-2009> to 1st dose		
<risk period>after 1st dose		
Control period after 1st dose		
<risk period>after 2nd dose		
Control period after 2nd dose		
Pooled control periods		
Pooled risk periods		

Notes: Risk period after Xst dose: <day0 to day30> after dose X

Control period after Xst dose: from <day31> after dose X until the day before next dose or until <31-Oct-2010>.

Table 12 Relative incidences (RI) in the case-series analysis after vaccination with Pandemrix™ in the <risk period> with adjustment for <the time since transplantation> (<pandemic influenza subset>)

Variable	Compared periods	Relative incidence	95% CI	
			LL	UL
Pandemrix™	<risk period> after any dose vs. other periods			
Time since transplantation	0-30 vs. >180 days			
	31-90 vs. >180 days			
	91-180 vs. >180 days			
	missing vs. >180 days			
<Covariate>				

95% CI = 95% percentile bootstrap confidence interval
LL =lower limit
UL=upper limit

Table 13 Relative incidences (RI) in the case series analysis after vaccination with Pandemrix™ in the <risk period> with adjustment for <the time since transplantation> (not accounting for perturbed post-event exposure) (<pandemic influenza subset>)

Variable	Compared periods	Relative incidence	95% CI	
			LL	UL
Pandemrix™	<risk period> after any dose vs. other periods			
Time since transplantation	0-30 vs. >180 days			
	31-90 vs. >180 days			
	91-180 vs. >180 days			
	missing vs. >180 days			
<Covariate>				

95% CI = 95% Wald confidence interval
LL =lower limit
UL=upper limit

Table 14 SOT rejections from 01-September to 31-August from any of the seasons 2006/2007, 2007/2008 and 2008/2009 in the <risk period> and control periods (<seasonal influenza subset>)

Period	Number of cases	Person*years
Control period before seasonal influenza vaccination		
<risk period> after seasonal influenza vaccination		
Control period after seasonal influenza vaccination		
Pooled control periods		
Pooled risk periods		

Notes: Risk periods after vaccination: <day0 to day30>
Control period after vaccination: from 01-September to seasonal influenza vaccination or from <day31> after vaccination until 31 August.

Table 15 Relative incidences (RI) in the case series analysis after seasonal influenza vaccination in the <risk period> with adjustment for <the time since transplantation> (<seasonal influenza subset>)

Variable	Compared periods	Relative incidence	95% CI	
			LL	UL
Seasonal influenza vaccination	0-30 days after vaccination vs. other periods			
Time since transplantation	0-30 vs. >180 days			
	31-90 vs. >180 days			
	91-180 vs. >180 days			
	missing vs. >180 days			
<Covariate>				

95% CI = 95% percentile bootstrap confidence interval
LL =lower limit
UL=upper limit

Table 16 Relative incidences (RI) in the case series analysis after seasonal influenza vaccination in the <risk period> with adjustment for <the time since transplantation> (not accounting for perturbed post-event exposure) (<seasonal influenza subset>)

Variable	Compared periods	Relative incidence	95% CI	
			LL	UL
Seasonal influenza vaccination	<0-30 days> after vaccination vs. other periods			
Time since transplantation	0-30 vs. >180 days			
	31-90 vs. >180 days			
	91-180 vs. >180 days			
	missing vs. >180 days			
<Covariate>				

95% CI = 95% Wald confidence interval
LL =lower limit
UL=upper limit

Appendix E: CPRD GOLD TRANSPLANTATION CODES (MEDCODES/ READ CODES)

READ code	medcode	Description	Organ type
"ZV42.00"	22653	[V]Transplanted organ or tissue	Global
"ZV42.11"	96423	[V]Transplanted organ	Global
"ZV42z00"	72092	[V]Unspecified transplanted organ or tissue	Global
"SP08.00"	44893	Transplanted organ complication	Global
"SP08z00"	25896	Transplanted organ complication NOS	Global
"ZV42y00"	66456	[V]Other specified transplanted organ or tissue	Global
'SP08A00'	99847	Post-transplant lymphoproliferative disorder	Global
"7900.00"	250	Transplantation of heart and lung	Heart and lung
"7900000"	53626	Allotransplantation of heart and lung	Heart and lung
"7900z00"	61073	Transplantation of heart and lung NOS	Heart and lung
"ZV59600"	36960	[V]Heart and lungs transplant status	Heart and lung
"7901.00"	4438	Other transplantation of heart	Heart
"7901000"	242	Allotransplantation of heart NEC	Heart
"7901100"	72939	Xenotransplantation of heart	Heart
"7901200"	58529	Implantation of prosthetic heart	Heart
"7901400"	70105	Revision of implantation of prosthetic heart	Heart
"7901500"	93844	Revision of transplantation of heart NEC	Heart
"7901y00"	69734	Other specified other transplantation of heart	Heart
"7901z00"	41495	Other transplantation of heart NOS	Heart
"ZV42100"	9384	[V]Heart transplanted	Heart
"TB00000"	64438	Heart transplant with complication, without blame	Heart
"7B00.00"	2997	Transplantation of kidney	Kidney
"7B00000"	55151	Autotransplant of kidney	Kidney
"7B00100"	11745	Transplantation of kidney from live donor	Kidney
"7B00111"	66705	Allotransplantation of kidney from live donor	Kidney
"7B00200"	24361	Transplantation of kidney from cadaver	Kidney
"7B00211"	98364	Allotransplantation of kidney from cadaver	Kidney
"7B00300"	89924	Allotransplantation of kidney from cadaver, heart-beating	Kidney
"7B00400"	96133	Allotransplantation kidney from cadaver, heart non-beating	Kidney
"7B00y00"	70874	Other specified transplantation of kidney	Kidney
"7B00z00"	5504	Transplantation of kidney NOS	Kidney
"ZV42000"	5911	[V]Kidney transplanted	Kidney
"TB00100"	54990	Kidney transplant with complication, without blame	Kidney
"TB00111"	18774	Renal transplant with complication, without blame	Kidney
"7800.00"	4405	Transplantation of liver	Liver
"7800000"	32025	Orthotopic transplantation of liver	Liver
"7800100"	71422	Heterotopic transplantation of liver	Liver
"7800111"	89445	Auxillary liver transplant	Liver
"7800112"	100073	Piggy back liver transplant	Liver
"7800200"	69194	Replacement of previous liver transplant	Liver
"7800500"	97157	Orthotopic transplantation of liver NEC	Liver

READ code	medcode	Description	Organ type
"7800y00"	99250	Other specified transplantation of liver	Liver
"7800z00"	27319	Transplantation of liver NOS	Liver
"ZV42700"	9026	[V]Liver transplanted	Liver
"TB00200"	31997	Liver transplant with complication, without blame	Liver
"7450.00"	10461	Transplantation of lung	Lung
"7450000"	96578	Double lung transplant	Lung
"7450100"	93713	Single lung transplant	Lung
"7450y00"	73743	Other specified transplantation of lung	Lung
"7450z00"	38011	Transplantation of lung NOS	Lung
"ZV42600"	10394	[V]Lung transplanted	Lung
"7830.00"	35368	Transplantation of pancreas	Pancreas
"7830100"	56993	Transplantation of whole pancreas	Pancreas
"7830200"	101231	Transplantation of tail of pancreas	Pancreas
"7830z00"	67499	Transplantation of pancreas NOS	Pancreas
"ZV42y12"	44077	[V]Pancreas transplanted	Pancreas
'7830300'	60955	Transplantation of islets of Langerhans	Pancreas

Appendix F: CPRD GOLD TRANSPLANT REJECTION CODES (MEDCODES/ READ CODES)

READ code	medcode	Description	Organ type
"SP08100"	11113	Transplanted organ rejection	Global
"SP08000"	29831	Transplanted organ failure	Global
"SyuKK00"	50226	[X]Failure & rejection of other transplanted organ & tissue	Global
"SP08400"	47484	Heart transplant failure and rejection	Heart
"SP08500"	27679	Heart-lung transplant failure and rejection	Heart and lung
"7B01511"	72004	Excision of rejected transplanted kidney	Kidney
"K0B5.00"	48057	Renal tubulo-interstitial disorders in transplant rejection	Kidney
"SP08300"	11553	Kidney transplant failure and rejection	Kidney
"Kyu1C00"	100693	[X]Renal tubulo-interstitial disorders/transplant rejection	Kidney
'7B01500'	48121	Transplant nephrectomy	Kidney
"SP08600"	6692	Liver transplant failure and rejection	Liver
"7831200"	96129	Excision of transplanted pancreas	Pancreas

Appendix G: ICD-10 TRANSPLANTATION CODES IN HES

ICD-10 code	Description	Organ type
Y830	Surgical operation with transplant of whole organ	Global
Z948	Other transplanted organ and tissue status	Global
Z949	Transplanted organ and tissue status, unspecified	Global
Z941	Heart transplant status	Heart
Z940	Kidney transplant status	Kidney
Z944	Liver transplant status	Liver
Z943	Heart and lungs transplant status	Heart and lung
Z942	Lung transplant status	Lung

Appendix H: ICD-10 TRANSPLANT REJECTION CODES IN HES

ICD-10 code	Description	Organ type
T868	Failure and reject of other transplanted organs and tissues	Global
T869	Failure and reject of unspec transplanted organ and tissue	Global
T862	Heart transplant failure and rejection	Heart
N165	Renal tubulo-interstitial disorders in transplant rejection	Kidney
T861	Kidney transplant failure and rejection	Kidney
T864	Liver transplant failure and rejection	Liver
T863	Heart-lung transplant failure and rejection	Heart and lung

Appendix I: OPCS 4 PROCEDURE CODES FOR TRANSPLANTATION

OPCS	Procedure description	Organ type
M01.1	Autotransplantation of kidney	Kidney
M01.2	Allotransplantation of kidney from live donor	Kidney
M01.3	Allotransplantation of kidney from cadaver NEC	Kidney
M01.4	Allotransplantation of kidney from cadaver heart beating	Kidney
M01.5	Allotransplantation of kidney from cadaver heart non-beating	Kidney
M01.8	Other specified transplantation of kidney	Kidney
M01.9	Unspecified transplantation of kidney	Kidney
M08.4	Exploration of transplanted kidney	Kidney
M17.4	Post-transplantation of kidney examination - recipient	Kidney
J01.1	Orthotopic transplantation of liver NEC	Liver
J01.2	Heterotopic transplantation of liver	Liver
J01.3	Replacement of previous liver transplant	Liver
J01.4	Transplantation of liver cells	Liver
J01.5	Orthotopic transplantation of whole liver	Liver
J01.8	Other specified transplantation of liver	Liver
J01.9	Unspecified transplantation of liver	Liver
K01.1	Allotransplantation of heart and lung	Heart and lung
K01.2	Revision of transplantation of heart and lung	Heart and lung
K01.8	Other specified transplantation of heart and lung	Heart and lung
K01.9	Unspecified transplantation of heart and lung	Heart and lung
K02.1	Allotransplantation of heart NEC	Heart
K02.2	Xenotransplantation of heart	Heart
K02.3	Implantation of prosthetic heart	Heart
K02.4	Piggyback transplantation of heart	Heart
K02.5	Revision of implantation of prosthetic heart	Heart
K02.6	Revision of transplantation of heart NEC	Heart
K02.8	Other specified other transplantation of heart	Heart
K02.9	Unspecified other transplantation of heart	Heart
E53.1	Double lung transplant	Lung
E53.2	Single lung transplant	Lung
E53.3	Single lobe lung transplant	Lung
E53.8	Other specified transplantation of lung	Lung
E53.9	Unspecified transplantation of lung	Lung
J54.1	Transplantation of pancreas and duodenum	Pancreas
J54.2	Transplantation of whole pancreas	Pancreas
J54.3	Transplantation of tail of pancreas	Pancreas
J54.4	Transplantation of islet of Langerhans	Pancreas
J54.5	Renewal of transplanted pancreatic tissue	Pancreas
J54.8	Other specified transplantation of pancreas	Pancreas
J54.9	Unspecified transplantation of pancreas	Pancreas

Appendix J: OPCS 4 PROCEDURE CODES FOR TRANSPLANT REJECTION

OPCS	Procedure description	Organ type
J55.3	Excision of transplanted pancreas	Pancreas
M02.6	Excision of rejected transplanted kidney	Kidney

Appendix K: ADDITIONAL CODES (READ CODES/ MEDCODES) TO FURTHER IDENTIFY UNSPECIFIED TRANSPLANTED ORGANS OR THE ORGAN RELATED TO A REJECTION EPISODE

Read Code	medcode	Description	Organ
9N1P.00	252	Seen in cardiac clinic	Heart
ZL9A300	7435	Seen by cardiologist	Heart
ZL9G300	30346	Seen by cardiac surgeon	Heart
14S3.00	59394	H/O: heart recipient	Heart
9N1m.11	5193	Seen in renal clinic	Kidney
9N1m.00	5212	Seen in nephrology clinic	Kidney
9N1l.00	6283	Seen in urology clinic	Kidney
ZL9AO00	10267	Seen by nephrologist	Kidney
ZL9GR00	10895	Seen by urologist	Kidney
14S2.00	49028	H/O: kidney recipient	Kidney
9N1Y.00	7178	Seen in gastroscopy clinic	Liver
9N1g.00	7198	Seen in gastroenterology clinic	Liver
ZL9GC00	28893	Seen by gastrointestinal surgeon	Liver
14S8.00	37198	H/O: liver recipient	Liver
9N0v.00	83491	Seen in liver clinic	Liver
ZL9A600	8269	Seen by respiratory physician	Lung
9N2g.00	18885	Seen by respiratory physician	Lung
ZL9G400	22429	Seen by thoracic surgeon	Lung
8I3b.00	26349	Spirometry test declined	Lung
14S9.00	65772	H/O: lung recipient	Lung
9N1s.00	7465	Seen in endocrine clinic	Pancreas
ZL5AC00	11886	Referral to endocrinologist	Pancreas
ZL9GB00	30585	Seen by endocrinology surgeon	Pancreas
8HVZ.00	32689	Private referral to endocrinologist	Pancreas
ZL5GI00	46893	Referral to endocrine surgeon	Pancreas

Appendix L: CPRD GOLD CODES (READ CODES/ MEDCODES AND PRODCODES) FOR INFLUENZA VACCINATION

1. H1N1 pandemic influenza vaccinations (Pandemrix™ and unknown manufacturers)

Immunisation Code	Description	Stage	Medcode	READ Code	Read Term
PFLUGEN	Influenza A H1N1v unknown brand	1	94301	65E0.00	First pandemic influenza vaccination
PFLUGEN	Influenza A H1N1v unknown brand	2	95092	65E1.00	Second pandemic influenza vaccination
PFLUGENO	Influenza A H1N1v unknown brand OHP	1	98217	65E3.00	1st pandemic influenza vacc give by other healthcare providr
PFLUGENO	Influenza A H1N1v unknown brand OHP	2	98306	65E4.00	2nd pandemic influenza vacc give by other healthcare providr
PFLUGSK	Influenza A H1N1v GSK PANDEMRIX	1	98183	65E9.00	PANDEMRIX - first influenza A (H1N1v) 2009 vaccination given
PFLUGSK	Influenza A H1N1v GSK PANDEMRIX	2	98184	65EA.00	PANDEMRIX - second influenza A (H1N1v) 2009 vaccination give
PFLUGSKO	Influenza A H1N1v OHP PANDEMRIX	1	98203	65EB.00	PANDEMRIX - 1st flu A (H1N1v) 2009 vac by othr hlth provider
PFLUGSKO	Influenza A H1N1v OHP PANDEMRIX	2	98304	65EC.00	PANDEMRIX - 2nd flu A (H1N1v) 2009 vac by othr hlth provider

prodcode for Therapy	BNF Code	Product Name	Drug Substance Name
41150	14040900	PANDEMRIX vaccine (GLAXSK UK)	Influenza virus vaccine
41168	14040900	Influenza (h1n1) inactivated split virion vaccine	Influenza virus vaccine

2. Seasonal influenza vaccination (all manufacturers)

Immunisation Code	Description in the CPRD	medcode	READ Code	Read Term
FLU	Influenza vaccination	6	65E..00	Influenza vaccination
FLU	Influenza vaccination given by other healthcare provider	97941	65E2.00	Influenza vaccination given by other healthcare provider

Prodcode for Therapy	BNF Code	Product Name	Drug Substance Name
1329	14040900	FLUVIRIN vaccine [NOVARTIS]	influenza virus surface antigen inactivated
639	14040900	influenza inactivated split virion vaccine	influenza virus split virion inactivated
922	14040900	influenza inactivated surface antigen vaccine	influenza virus surface antigen inactivated
2552	14040900	INFLUVAC SUB-UNIT vaccine [ABBOTT]	influenza virus surface antigen inactivated
2601	14040900	MFV-JECT vaccine [AV/PASTEUR]	influenza virus split virion inactivated
2139	14040900	FLUARIX vaccine [GLAXSK PHA]	influenza virus split virion inactivated
834	14040900	BEGRIVAC vaccine [NOVARTIS]	influenza virus split virion inactivated
398	140409	INFLUENZA INACTIVATED SPLIT VIRION	influenza virus split virion

Prodcode for Therapy	BNF Code	Product Name	Drug Substance Name
	00	vaccine [AV/PASTEUR]	inactivated
13595	14040900	FLUZONE vaccine [AV/PASTEUR]	influenza virus split virion inactivated
11824	14040900	ENZIRA vaccine [WYETH PHAR]	influenza virus split virion inactivated
27407	14040900	IMUVAC vaccine [ABBOTT]	influenza virus surface antigen inactivated
9710	14040900	AGRIPPAL vaccine [NOVARTIS]	influenza virus surface antigen inactivated
18612	14040900	MASTAFLU vaccine [MASTA]	influenza virus surface antigen inactivated
10030	14040900	INFLEXAL V vaccine [MASTA]	influenza virus surface antigen inactivated
16585	14040900	VIROFLU vaccine [CRUCELL]	influenza virus surface antigen inactivated
43825	14040900	INTANZA vaccine 15micrograms [SAN PAST]	influenza virus split virion inactivated
30198	14040900	INFLUENZA INACTIVATED SPLIT VIRION vaccine [SAN PAST]	influenza virus split virion inactivated
40760	14040900	influenza inactivated split virion vaccine 15micrograms	influenza virus split virion inactivated
43827	14040900	INTANZA vaccine 9micrograms [SAN PAST]	influenza virus split virion inactivated
32391	14040900	INFLUENZA INACTIVATED SURFACE ANTIGEN vaccine [NOVARTIS]	influenza virus surface antigen inactivated
30156	14040900	INVIVAC vaccine [SOLVAY]	influenza virus surface antigen inactivated
40876	14040900	influenza inactivated split virion vaccine 9micrograms	influenza virus split virion inactivated
24779	14040900	influenza inactivated split virion paediatric vaccine	influenza virus split virion inactivated
38421	14040900	INFLUENZA INACTIVATED SPLIT VIRION vaccine [EVANS VAC]	influenza virus split virion inactivated
45661	14040900	INFLUENZA INACTIVATED SPLIT VIRION vaccine [WYETH PHAR]	influenza virus split virion inactivated

Appendix M: CPRD GOLD CODES (READ CODES/ MEDCODES) FOR INFECTIONS AND CHRONIC CONDITIONS

1. Respiratory infections

1.1. Influenza/ Influenza like illness

READ code	medcode	description
16L..00	8980	Influenza-like symptoms
460 C	75038	[1]Influenza-like illness‡
470	74978	Influenza‡
470 F	74058	Flu‡
471	83036	Pneumonia influenzal‡
472 A	79202	Influenzal bronchitis‡
472 H	89610	Influenza haemorrhagic‡
473	76318	Influenza gastric‡
473 E	89847	Influenzal enteritis‡
A08..11	6046	Gastric flu
H2...00	10086	Pneumonia and influenza
H27..00	556	Influenza
H270.00	15912	Influenza with pneumonia
H270.11	29457	Chest infection - influenza with pneumonia
H270000	13573	Influenza with bronchopneumonia
H270100	62632	Influenza with pneumonia, influenza virus identified
H270z00	35745	Influenza with pneumonia NOS
H271.00	43625	Influenza with other respiratory manifestation
H271000	15774	Influenza with laryngitis
H271100	29617	Influenza with pharyngitis
H271z00	23488	Influenza with respiratory manifestations NOS
H27y.00	47472	Influenza with other manifestations
H27y000	46157	Influenza with encephalopathy
H27y100	14791	Influenza with gastrointestinal tract involvement
H27yz00	31363	Influenza with other manifestations NOS
H27z.00	16388	Influenza NOS
H27z.11	2157	Flu like illness
H27z.12	5947	Influenza like illness
H29..00	94930	Avian influenza
H2A..00	98129	Influenza due to Influenza A virus subtype H1N1
H2A..11	98102	Influenza A (H1N1) swine flu
H2y..00	11849	Other specified pneumonia or influenza
H2z..00	6094	Pneumonia or influenza NOS

‡Descriptions of READ codes kindly provided by the authors (Stowe et al., 2008)

1.2. Tuberculosis

Read Code	Medical code	Description

Read Code	Medical code	Description
1411.00	5319	H/O: tuberculosis
14P9.00	100469	History of tuberculosis drug therapy
65V9.00	32180	Notification of tuberculosis
65V9.11	16582	TB - tuberculosis notification
65Y..00	11819	Tuberculosis status
65Y2.00	91666	Streptomycin resistant tuberculosis
65Y8.00	97525	Ciprofloxacin resistant tuberculosis
65Y9.00	96477	Inactive tuberculosis
65Y9.11	95913	Latent tuberculosis
69A3.00	36841	Exam. for suspected TB
745F.00	85954	Tuberculosis support
745F200	91292	Directly observed therapy
8BAD100	4247	TB chemotherapy
A1...00	1840	Tuberculosis
A10..00	22011	Primary tuberculous infection
A100.00	16265	Primary tuberculous complex
A101.00	46272	Tuberculous pleurisy in primary progressive tuberculosis
A10y.00	42630	Other primary progressive tuberculosis
A10z.00	37694	Primary tuberculous infection NOS
A11..00	635	Pulmonary tuberculosis
A11..11	47336	Lung tuberculosis
A110.00	53701	Infiltrative lung tuberculosis
A111.00	48580	Nodular lung tuberculosis
A112.00	16331	Tuberculosis of lung with cavitation
A113.00	62468	Tuberculosis of bronchus
A114.00	16741	Tuberculous fibrosis of lung
A115.00	15693	Tuberculous bronchiectasis
A116.00	9953	Tuberculous pneumonia
A117.00	66441	Tuberculous pneumothorax
A11y.00	18950	Other specified pulmonary tuberculosis
A11z.00	38110	Pulmonary tuberculosis NOS
A12..00	63959	Other respiratory tuberculosis
A120.00	23472	Tuberculous pleurisy
A120000	37834	Tuberculosis of pleura
A120100	39512	Tuberculous empyema
A120200	14913	Tuberculous hydrothorax
A120z00	56890	Tuberculous pleurisy NOS
A121.00	58827	Tuberculosis of intrathoracic lymph nodes
A121000	5145	Tuberculosis of hilar lymph nodes
A121100	44129	Tuberculosis of mediastinal lymph nodes
A121200	49503	Tuberculosis of tracheobronchial lymph nodes
A121z00	46926	Tuberculosis of intrathoracic lymph nodes NOS
A122.00	69260	Isolated tracheal or bronchial tuberculosis
A122000	93015	Isolated tracheal tuberculosis
A122100	93948	Isolated bronchial tuberculosis
A122z00	53473	Isolated tracheal or bronchial tuberculosis NOS

Read Code	Medical code	Description
A123.00	20333	Tuberculous laryngitis
A124.00	31670	Resp TB bacteriologically and histologically confirmed
A124000	24413	TB lung confirm sputum microscopy with or without culture
A124100	93071	Tuberculosis of lung, confirmed by culture only
A124200	62530	Tuberculosis of lung, confirmed histologically
A124300	58588	Tuberculosis of lung, confirmed by unspecified means
A124400	44655	TB intrathoracic lymph nodes confirm bact histologically
A124500	44039	Tuberculosis of larynx, trachea & bronchus conf bact/hist'y
A124600	35443	Tuberculous pleurisy, conf bacteriologically/histologically
A124700	24517	Primary respiratory TB confirm bact and histologically
A125.00	7133	Respiratory TB not confirmed bact or histologically
A125000	47832	Tuberculosis of lung, bacteriologically & histolog'y neg
A125200	40605	Prim respiratory TB without mention of bact or hist confirm
A125X00	69471	Resp TB unspcf,w'out mention/bacterial or histol confrmtn
A12y.00	50902	Other specified respiratory tuberculosis
A12y000	37598	Tuberculosis of mediastinum
A12y100	72402	Tuberculosis of nasopharynx
A12y200	97658	Tuberculosis of nasal septum
A12y300	45861	Tuberculosis of nasal sinus
A12yz00	50147	Other specified respiratory tuberculosis NOS
A13..00	41208	Tuberculosis of meninges and central nervous system
A130.00	11975	Tuberculous meningitis
A130000	54840	Tuberculosis of cerebral meninges
A130100	46802	Tuberculosis of spinal meninges
A130300	43791	Tuberculous meningoencephalitis
A130z00	69322	Tuberculous meningitis NOS
A133.00	57398	Tuberculous abscess of brain
A135.00	46044	Tuberculous abscess of spinal cord
A136.00	59202	Tuberculous encephalitis or myelitis
A136000	93360	Tuberculous encephalitis
A136100	31680	Tuberculous myelitis
A136z00	72072	Tuberculous encephalitis or myelitis NOS
A13y.00	41383	Other specified tuberculosis of central nervous system
A13z.00	70140	Tuberculosis of central nervous system NOS
A14..00	2193	Tuberculosis of intestines, peritoneum and mesenteric glands
A140.00	31409	Tuberculous peritonitis
A14y.00	54570	Other gastrointestinal tract tuberculosis
A14y100	39279	Tuberculosis of large intestine
A14y200	31436	Tuberculosis of small intestine
A14y300	29482	Tuberculosis of mesenteric lymph glands
A14y400	59087	Tuberculosis of rectum
A14y500	49433	Tuberculosis of retroperitoneal lymph nodes
A14yz00	33372	Other gastrointestinal tract tuberculosis NOS
A14z.00	54579	Tuberculosis of gastrointestinal tract NOS
A15..00	3596	Tuberculosis of bones and joints
A15..11	22572	Tuberculous osteomylelytis

Read Code	Medical code	Description
A15..12	24626	Tuberculous arthritis
A15..13	45318	Tuberculous synovitis
A150.00	3273	Tuberculosis of vertebral column - Pott's
A151.00	2208	Tuberculosis of hip
A152.00	23451	Tuberculosis of knee
A153.00	4907	Tuberculosis limb bones - Tuberculous dactylitis
A154.00	17153	Tuberculous mastoiditis
A15x.00	37886	Tuberculosis of other specified bones
A15y.00	42201	Tuberculosis of other specified joint
A15z.00	44128	Tuberculosis of bones or joints NOS
A16..00	37422	Tuberculosis of genitourinary system
A160.00	3303	Tuberculosis of kidney
A160.11	23940	Renal tuberculosis
A160000	52272	Tuberculous nephropathy
A160100	50837	Tuberculous pyelitis
A160200	49235	Tuberculous pyelonephritis
A160z00	67292	Tuberculosis of kidney NOS
A161.00	3830	Tuberculosis of bladder
A162.00	53548	Tuberculosis of ureter
A163.00	34657	Tuberculosis of other urinary organs
A164.00	27399	Tuberculosis of epididymis
A165.00	68821	Tuberculosis of other male genital organs
A165000	60040	Tuberculosis of prostate
A165100	49481	Tuberculosis seminal vesicle
A165200	30945	Tuberculosis of testis
A165z00	69154	Tuberculosis of other male genital organs NOS
A166.00	57466	Tuberculous oophoritis or salpingitis
A166000	72743	Tuberculous oophoritis
A166100	38920	Tuberculous salpingitis
A166111	31349	Fallopian tube tuberculosis
A166z00	63796	Tuberculous oophoritis or salpingitis NOS
A167.00	66584	Tuberculosis of other female genital organs
A167000	49112	Tuberculous cervicitis
A167100	12448	Tuberculous endometritis
A167z00	68973	Tuberculosis of other female genital organs NOS
A168.00	50489	Tuberculosis of urinary tract
A16z.00	50261	Genitourinary tuberculosis NOS
A17..00	55835	Tuberculosis of other organs
A170.00	47881	Tuberculosis of skin and subcutaneous tissue
A170.11	46675	Lupus - tuberculous
A170000	67637	Tuberculosis - lupus exedens
A170100	16367	Tuberculosis - lupus vulgaris
A170200	47430	Tuberculosis - scrofuloderma
A170300	37492	Tuberculosis - lupus NOS
A170500	63351	Tuberculosis cutis
A170600	4621	Tuberculosis lichenoides

Read Code	Medical code	Description
A170700	62033	Tuberculosis papulonecrotica
A170800	31445	Tuberculosis verrucosa cutis
A170z00	30687	Tuberculosis of skin and subcutaneous tissue NOS
A171.00	44573	Tuberculosis with erythema nodosum hypersensitivity reaction
A171000	23962	Bazin's disease - erythema induratum - TB hypersensitivity
A171100	34640	Tuberculous erythema nodosum
A171z00	56833	Erythema nodosum with tuberculosis NOS
A172.00	4256	Tuberculosis of peripheral lymph nodes
A172000	3720	Tuberculous - cervical lymphadenitis
A172011	40522	Scrofula - tuberculous cervical lymph nodes
A172100	51110	Scrofulous tuberculous abscess
A172200	5101	Tuberculous adenitis
A172z00	26344	Tuberculosis of peripheral lymph nodes NOS
A173.00	43976	Tuberculosis of eye
A173000	37329	Tuberculous chorioretinitis
A173100	19652	Tuberculous episcleritis
A173200	55629	Tuberculous interstitial keratitis
A173300	38342	Tuberculous chronic iridocyclitis
A173400	30358	Tuberculous keratoconjunctivitis
A173z00	70491	Tuberculosis of eye NOS
A174.00	58673	Tuberculosis of ear
A175.00	73590	Tuberculosis of thyroid gland
A176.00	35760	Tuberculosis of adrenal glands - Addison's disease
A177.00	66976	Tuberculosis spleen
A178.00	56670	Tuberculosis oesophagus
A17y.00	46727	Tuberculosis of other specified organs
A17y000	96668	Tuberculosis endocardium
A17y100	50869	Tuberculosis myocardium
A17y200	40231	Tuberculosis pericardium
A17y300	46019	Tuberculosis of stomach
A17y400	46147	Tuberculosis of liver
A17yz00	46383	Tuberculosis of other specified organs NOS
A17z.00	45932	Tuberculosis of other organs NOS
A18..00	16414	Miliary tuberculosis
A180.00	72008	Acute miliary tuberculosis
A180000	31844	Acute miliary tuberculosis of a single specified site
A180100	42479	Acute miliary tuberculosis of multiple sites
A18y.00	32459	Other specified miliary tuberculosis
A18z.00	53331	Miliary tuberculosis NOS
A1y..00	34430	Other specified tuberculosis
A1z..00	15158	Tuberculosis NOS
AE0..00	29395	Late effects of tuberculosis
AE00.00	65464	Late effects of respiratory tuberculosis
AE01.00	73273	Late effects of central nervous system tuberculosis
AE02.00	40990	Late effects of genitourinary system tuberculosis
AE03.00	73549	Late effects of tuberculosis of bones and joints

Read Code	Medical code	Description
AE04.00	70911	Late effects of tuberculosis of other specified organs
AE0z.00	61442	Late effects of tuberculosis NOS
Ayu1.00	73149	[X]Tuberculosis
Ayu1000	73185	[X]Other resp tubercul,confirmd bacteriologicly+histologicly
Ayu1100	73225	[X]Resp tuberculos unspcfd,confirmd bacteriolog+histologicly
Ayu1300	55298	[X]Resp TB unspcf,w'out mention/bacterial or histol confrmtn
Ayu1600	72680	[X]Tuberculosis of other specified organs
Ayu1900	97922	[X]Miliary tuberculosis, unspecified
AyuJ400	93768	[X]Sequelae of respiratory and unspecified tuberculosis
AyuJ500	97866	[X]Sequelae of poliomyelitis
AyuJ900	101954	[X]Sequelae of viral hepatitis
F004.00	11976	Meningitis - tuberculous
F033300	99925	Encephalitis due to tuberculosis
F033311	97778	Tuberculous encephalitis
F040600	54908	Tuberculous intracranial abscess
F4A5500	94249	Keratitis due to tuberculosis
G500300	57126	Acute pericarditis - tuberculous
G500311	16996	TB - acute pericarditis
G520600	91847	Acute myocarditis - tuberculous
H450.00	63172	Pneumoconiosis associated with tuberculosis
H510.00	23482	Pleurisy without effusion or active tuberculosis
H510900	32818	Pneumococcal pleurisy
H510z00	31645	Pleurisy without effusion or active tuberculosis NOS
J550200	32899	Peritonitis - tuberculous
K154800	56771	Cystitis in tuberculosis
K43..00	27611	Female tuberculous pelvic inflammatory disease
L173.00	99188	Maternal tuberculosis in pregnancy/childbirth/puerperium
L173000	58140	Maternal tuberculosis,unspec whether in pregnancy/puerperium
N018.00	97588	Tuberculous arthritis
N304.00	43370	Tuberculosis of spine (Pott's)
N304.11	6553	Tuberculosis of spine
N304000	70293	Tuberculosis of cervical spine
N304100	67337	Tuberculosis of thoracic spine
N304200	65994	Tuberculosis of lumbar spine
N304300	97325	Tuberculosis of sacrum/coccyx
N305.00	24372	Tuberculosis of limb bones
N305000	99914	Tuberculosis of unspecified limb bone
N305100	62963	Tuberculosis of the upper arm bone
N305200	68154	Tuberculosis of the forearm bone
N305300	59916	Tuberculosis of the pelvic and thigh bones
N305400	57587	Tuberculosis of the lower leg bone
N305500	95332	Tuberculosis of other limb bones
N306.00	12338	Tuberculosis of other bones
N306000	99305	Tuberculosis of bone, site unspecified
N306100	53864	Tuberculosis of the bones of the shoulder region

Read Code	Medical code	Description
N306200	99783	Tuberculosis of the bones of the hand
N306300	67601	Tuberculosis of the bones of the ankle and foot
N306400	71138	Tuberculosis of the bones of other sites
N306500	99593	Tuberculosis of the bones of multiple sites
N306z00	70862	Tuberculosis of bone NOS
ZV12A00	18206	[V] Personal history of pulmonary tuberculosis
ZV12B00	9158	[V] Personal history of tuberculosis
ZV71200	32925	[V]Observation for suspected tuberculosis
ZV71211	7898	[V]Observation for suspected tuberculosis (TB)

1.3. Pneumococcal infection

Read Code	Medical code	Description
A382.00	7787	Pneumococcal septicaemia
A3B2.00	5534	Pneumococcal infection
F001.00	4605	Pneumococcal meningitis
G50z200	36496	Acute pericarditis - pneumococcal
H023000	92428	Acute pneumococcal pharyngitis
H035000	58188	Acute pneumococcal tonsillitis
H060600	9043	Acute pneumococcal bronchitis
H21..00	1849	Lobar (pneumococcal) pneumonia
H21..11	29166	Chest infection - pneumococcal pneumonia
H510900	32818	Pneumococcal pleurisy
H511000	43345	Pneumococcal pleurisy with effusion
J551.00	47355	Pneumococcal peritonitis
N010900	66696	Pneumococcal arthritis and polyarthritis

1.4. Respiratory Syncytial Virus (RSV)

Read Code	Medical code	Description
4JU9.00	96556	Respiratory syncytial virus A detected
4JUA.00	96323	Respiratory syncytial virus B detected
4JUB.00	96052	Respiratory syncytial virus untyped strain detected
7Q05300	96192	RSV treatment and Hepatitis C treatment drugs Band 1
A79A.00	12573	Respiratory syncytial virus infection
H060D00	48593	Acute bronchitis due to respiratory syncytial virus
H061.00	1019	Acute bronchiolitis
H061000	54533	Acute capillary bronchiolitis
H061100	41589	Acute obliterating bronchiolitis
H061200	17185	Acute bronchiolitis with bronchospasm
H061300	69192	Acute exudative bronchiolitis
H061400	6181	Obliterating fibrous bronchiolitis
H061500	18451	Acute bronchiolitis due to respiratory syncytial virus
H061600	66228	Acute bronchiolitis due to other specified organisms
H061z00	17917	Acute bronchiolitis NOS
H201.00	31269	Pneumonia due to respiratory syncytial virus

2. Acute bacterial infections

2.1. Pseudomonas

Read Code	Medical code	Description
43nB.00	95821	Pseudomonas antibody level
A074100	54552	Pseudomonas gastrointestinal tract infection
A074111	56957	Diarrhoea due to Pseudomonas pyocyanea
A384300	12400	Pseudomonas septicaemia
A3B7.00	6856	Pseudomonas infection
A3BXF00	45692	Pseudomonas as cause/diseases classifd to other chapters
F00y600	90288	Meningitis due to pseudomonas
F00y611	52697	Pseudomonas meningitis
H221.00	30591	Pneumonia due to pseudomonas

2.2. Clostridium difficile

Read Code	Medical code	Description
4JD2000	10716	Clostridium difficile toxin A detected
A3Ay200	6700	Clostridium difficile infection
A3Ayz00	41635	Other specified bacterial disease NOS

3. Chronic viral infections

3.1. HIV/ AIDS

Read Code	Medical code	Description
43C3.11	2835	HIV positive
43w3.00	93642	Human immunodeficiency virus RNA/DNA ratio
4J34.00	27053	HIV viral load
4J3F.00	96902	Human immunodeficiency virus viral load by log rank

3.2. Viral hepatitis B and C

Read Code	Medical code	Description
43B5.00	27174	Hepatitis e antigen present
43M2.00	27250	Hepatitis A test positive
43X3.00	28568	Hepatitis C antibody test positive
43dC.00	12087	Hepatitis B e antibody level
4J3B.00	30884	Hepatitis C viral load
4J3D.00	56066	Hepatitis B viral load
4JQ3.00	35589	Hepatitis C virus genotype
4JQD.00	102568	Hepatitis C viral ribonucleic acid PCR positive
4JQD.11	102565	Hepatitis C PCR positive

4. Opportunistic infections

4.1. Cytomegalovirus (CMV)

Read Code	Medical code	Description
65O7.00	39680	Anti-CMV i-v immunoglobulin

Read Code	Medical code	Description
A785.00	43622	Cytomegalic inclusion disease
A785000	45072	Cytomegaloviral pneumonitis
A785100	44278	Cytomegaloviral pancreatitis
A785200	34087	Cytomegaloviral hepatitis
A785X00	9296	Cytomegaloviral disease, unspecified
F030700	97267	Encephalitis due to cytomegalovirus
F030711	68273	Cytomegaloviral encephalitis
H241.00	43286	Pneumonia with cytomegalic inclusion disease
J631100	4406	Hepatitis in cytomegalic inclusion virus
Q401.00	19584	Congenital cytomegalovirus infection

4.2. Herpes Simplex Virus (HSV)

Read Code	Medical code	Description
2524.00	15791	O/E-herpes labialis-cold sore
2524.11	9002	O/E - cold sore
2524.12	8248	O/E - herpes labialis
65PQ.00	32928	Genital herpes simplex contact
9kF8.00	96171	Treatment of recurrent genital herpes - enhanced services ad
9kF8.11	95905	Treatment of recurrent genital herpes
A54..00	548	Herpes simplex
A54..11	21408	Herpes simplex viral infection
A54..12	29956	Scrum pox
A541.00	946	Genital herpes simplex
A541000	15966	Genital herpes unspecified
A541100	11957	Herpetic vulvovaginitis
A541200	16488	Herpetic ulceration of vulva
A541300	21755	Herpetic infection of penis
A541400	6270	Herpesviral infection of perianal skin and rectum
A541500	17250	Anogenital herpesviral infection
A541600	96106	Genital herpes simplex type 1
A541700	96197	Genital herpes simplex type 2
A541800	96826	Recurrent genital herpes simplex type 1
A541900	96006	Recurrent genital herpes simplex type 2
A541z00	20617	Genital herpes simplex NOS
A544.00	1083	Ophthalmic herpes simplex
A544000	5078	Unspecified ophthalmic herpes
A544100	17500	Herpes simplex eyelid dermatitis
A544200	10408	Herpes simplex dendritic keratitis
A544300	1082	Herpes simplex disciform keratitis
A544400	61223	Herpes simplex iridocyclitis
A544500	43334	Herpes simplex ophthalmicus
A544z00	40712	Ophthalmic herpes simplex NOS
A545.00	48716	Herpes simplex septicaemia
A546.00	22269	Herpes simplex whitlow
A548.00	16925	[X] Herpes labialis
A54x.00	34295	Herpes simplex with other specified complication

Read Code	Medical code	Description
A54x000	55620	Visceral herpes simplex
A54x100	45009	Herpes simplex meningitis
A54x200	32206	Herpes simplex otitis externa
A54x300	17131	Herpesviral vesicular dermatitis
A54x400	47973	Herpes simplex pneumonia
A54xz00	36233	Herpes simplex with other specified complication NOS
A54y.00	24531	Herpes simplex with unspecified complication
A54z.00	29824	Herpes simplex no complication NOS
A54z.11	1601	Herpes labialis
AB05.11	25123	Herpes circinatus
Ayu4G00	97589	[X]Anogenital herpes viral infection, unspecified
F011300	54321	Meningitis due to herpes simplex virus
F011311	45182	Herpes simplex meningitis
F030400	54934	Encephalitis due to herpes simplex virus
F030411	41245	Herpes simplex encephalitis
F501500	67338	Infective otitis externa due to herpes simplex
F501511	48648	Herpes simplex- otitis externa

4.3. Varicella Zoster Virus (VZV)

Read Code	Medical code	Description
A52..00	145	Chickenpox - varicella
A52..11	1764	Chickenpox
A521.00	25462	Varicella pneumonitis
A52x.00	20400	Varicella with other specified complications
A52y.00	58869	Varicella with unspecified complications NOS
A52z.00	30473	Varicella with no complication NOS
A53..00	390	Herpes zoster
A53..11	516	Shingles
A530.00	44944	Herpes zoster with meningitis
A531.00	52126	Herpes zoster with other central nervous system complication
A531.11	1598	Post-herpetic neuralgia
A531000	50537	Herpes zoster with other CNS complications
A531100	27403	Geniculate herpes zoster
A531111	7331	Ramsey - Hunt syndrome
A531400	47375	Zoster encephalitis
A531z00	63739	Herpes zoster with other CNS complication NOS
A532.00	14718	Herpes zoster with ophthalmic complication
A532000	25320	Herpes zoster with dermatitis of eyelid
A532100	27546	Herpes zoster with keratoconjunctivitis
A532200	55940	Herpes zoster iridocyclitis
A532300	8936	Ophthalmic herpes zoster infection
A532400	18918	Herpes zoster ophthalmicus
A532z00	33810	Herpes zoster with other ophthalmic complication
A53x.00	43235	Herpes zoster with other specified complication
A53x000	14793	Herpes zoster otitis externa
A53x100	52319	Disseminated zoster

Read Code	Medical code	Description
A53xz00	38531	Herpes zoster with other specified complication NOS
A53y.00	21069	Herpes zoster with unspecified complication
A53z.00	21471	Herpes zoster NOS
AyuA300	70223	[X]Varicella without complications
AyuA500	70197	[X]Zoster without complications
F011200	71464	Meningitis due to herpes zoster virus
F011211	57895	Herpes zoster meningitis
F011300	54321	Meningitis due to herpes simplex virus
F011311	45182	Herpes simplex meningitis
F011700	43411	Varicella meningitis
F030900	51692	Encephalitis due to herpes zoster
F030911	69405	Herpes zoster encephalitis
F035000	42730	Encephalitis following chickenpox
F035011	51384	Encephalitis due to varicella
F037000	92694	Varicella transverse myelitis
F374400	39692	Polyneuropathy in herpes zoster
F501600	62558	Infective otitis externa due to herpes zoster
F501611	31681	Herpes zoster - otitis externa
H24y700	23726	Pneumonia with varicella

4.4. Epstein-Barr Virus (EBV)

Read Code	Medical code	Description
4J3E.00	87855	Epstein-Barr virus viral load
A79y.11	8359	Epstein-Barr virus
C396.00	56108	Immunodef follow hereditary defect respon Epstein-Barr vir

4.5. Pneumocystis

Read Code	Medical code	Description
A789300	27641	HIV disease resulting in Pneumocystis carinii pneumonia
AD63.00	35220	Pneumocystosis
H24y200	27519	Pneumonia with pneumocystis carinii

4.6. BK Virus (BKV)

Read Code	Medical code	Description
43jR.00	66181	BK virus nucleic acid detectn

4.7. Aspergillus

Read Code	Medical code	Description
AB63.00	17525	Aspergillosis
AB63000	42758	Invasive pulmonary aspergillosis
AB63100	16543	Tonsillar aspergillosis
AB63200	102517	Disseminated aspergillosis
AB63300	100742	Allergic bronchopulmonary aspergillosis
AB63400	11440	Pulmonary aspergillus disease
AB63500	100500	Aspergilloma

Read Code	Medical code	Description
AB63600	100650	Aspergillus bronchitis
AB63X00	40352	Aspergillosis, unspecified
AyuEK00	97915	[X]Other forms of aspergillosis
AyuEU00	96332	[X]Other pulmonary aspergillosis
F501B00	20815	Chronic otitis externa due to aspergillosis
H246.00	34274	Pneumonia with aspergillosis

4.8. Cryptococcus

Read Code	Medical code	Description
43f5.00	47458	Cryptococcus antigen level
AB65.00	36415	Cryptococcosis
AB65.11	49275	Busse - Buschke's disease
AB65.13	57579	Torula
AB65000	54906	Pulmonary cryptococcosis
AB65100	72181	Systemic cryptococcosis
AB65200	69547	Cryptococcal meningitis
AB65400	98248	Cerebral cryptococcosis
AB65500	95017	Cutaneous cryptococcosis
AB65600	69732	Osseous cryptococcosis
AB65z00	73425	Cryptococcosis NOS
F010.00	61657	Meningitis due to fungal organisms
F010000	31983	Meningitis due to cryptococcus

4.9. Listeria

Read Code	Medical code	Description
A270.00	33371	Listeriosis
A270000	51661	Listeria infection
A270100	52014	Listeria septicaemia
A270200	94781	Cutaneous listeriosis
A270300	50725	Listerial cerebral arteritis
A270400	24765	Listerial endocarditis
A270z00	99699	Listeriosis NOS
Ayu3500	99064	[X]Listeriosis, unspecified
F007100	50873	Meningitis due to listeriosis

4.10. Nocardia

Read Code	Medical code	Description
A39y.00	68400	Other specified actinomycosis
A39y000	73340	Pulmonary nocardiosis
A39y100	67378	Cutaneous nocardiosis
A39z.00	48569	Actinomycosis unspecified site
A39z000	61704	Maduromycosis NOS
A39z100	29026	Nocardiosis NOS
A39zz00	57668	Actinomycosis unspecified site NOS
G33z.00	25842	Angina pectoris NOS

Read Code	Medical code	Description
G33z000	66388	Status anginosus
G33z100	54535	Stenocardia
G33z200	7696	Syncope anginosa
G33z300	1414	Angina on effort
G33z400	32450	Ischaemic chest pain
G33z500	9555	Post infarct angina
G33z600	26863	New onset angina
G33z700	12804	Stable angina
G33zz00	28554	Angina pectoris NOS
H24y.00	69782	Pneumonia with other infectious diseases EC
H24y000	61623	Pneumonia with actinomycosis
H24y100	67901	Pneumonia with nocardiasis
H24y200	27519	Pneumonia with pneumocystis carinii
H24y300	60482	Pneumonia with Q-fever
H24y400	72182	Pneumonia with salmonellosis
H24y500	98782	Pneumonia with toxoplasmosis
H24y600	49398	Pneumonia with typhoid fever
H24y700	23726	Pneumonia with varicella
H24yz00	70559	Pneumonia with other infectious diseases EC NOS

4.11. Toxoplasma

Read Code	Medical code	Description
43E9000	44193	Raised toxoplasma titre
AD0..00	3084	Toxoplasmosis
AD00.00	51962	Toxoplasma meningoencephalitis
AD01.00	44971	Toxoplasma conjunctivitis
AD02.00	31619	Toxoplasma chorioretinitis
AD04.00	56762	Toxoplasma pneumonitis
AD05.00	66185	Toxoplasma hepatitis
AD0x.00	61091	Other specified site toxoplasma
AD0y.00	66547	Toxoplasmosis of multiple sites
AD0z.00	33697	Toxoplasmosis NOS
AyuFB00	100042	[X]Toxoplasmosis with other organ involvement
AyuFC00	98092	[X]Toxoplasmosis, unspecified
F033400	66247	Encephalitis due to toxoplasmosis
F033411	47634	Toxoplasmosis encephalitis
G520500	67291	Acute myocarditis - toxoplasmosis
G520600	91847	Acute myocarditis - tuberculous
H24y500	98782	Pneumonia with toxoplasmosis

4.12. Strongyloides

Read Code	Medical code	Description
43g9.00	33263	Strongyloides antibody level

4.13. Leishmania

Read Code	Medical code	Description
A85..00	4926	Leishmaniasis
A850.00	64252	Visceral leishmaniasis
A850.11	54758	Dumdum fever
A850.12	34721	Kala-azar
A851.00	27308	Urban cutaneous leishmaniasis
A851000	38643	Aleppo boil
A851100	38676	Baghdad boil
A851200	40312	Delhi boil
A851z00	98199	Urban cutaneous leishmaniasis NOS
A852.00	46811	Asian desert cutaneous leishmaniasis
A853.00	96093	Ethiopian cutaneous leishmaniasis
A854.00	42834	American cutaneous leishmaniasis
A85z.00	38324	Leishmaniasis NOS

4.14. Trypanosoma

Read Code	Medical code	Description
A86..00	34650	Trypanosomiasis
A86..11	28473	Sleeping sickness
A860.00	44049	Chagas' disease with heart involvement
A861.00	59402	Chagas' disease with other organ involvement
A861000	49477	Chagas' disease with digestive system involvement
A862.00	59618	Chagas' disease without mention of organ involvement
A863.00	60386	Gambian trypanosomiasis
A86z.00	88643	Trypanosomiasis NOS
F012.00	72646	Meningitis due to trypanosomiasis
F032100	97992	Encephalitis due to trypanosomiasis
J100000	69752	Megaoesophagus in Chagas' disease

4.15. Candida

Read Code	Medical code	Description
A789200	23951	HIV disease resulting in candidiasis
AB2..00	490	Candidiasis
AB2..11	2275	Moniliasis
AB24.00	48481	Candidiasis of lung
AB24.11	40299	Pneumonia - candidal
AB25.00	9230	Disseminated, systemic candida
AB2y.00	42550	Other specified candidiasis
AB2y000	24695	Candidal endocarditis
AB2y200	63388	Candidal meningitis
AB2y300	33717	Candidal septicaemia
AB2yz00	15719	Other specified candidiasis NOS
AB2yz11	40948	Monilial granuloma
AB2yz12	45186	Intestinal moniliasis
AB2yz16	50088	Intestinal candidiasis

Read Code	Medical code	Description
AB2z.00	16532	Candidiasis NOS
AyuE400	73114	[X]Candidiasis of other sites
AyuE500	53911	[X]Candidiasis, unspecified
H247000	52071	Pneumonia with candidiasis
Q407500	55689	Neonatal candida septicaemia
Q407511	95112	Neonatal monilial septicaemia

Appendix N: CPRD GOLD CODES FOR MALIGNANCIES/ CANCERS

Medical code	Read Code	Description
6230	1425.00	H/O: * skin
7761	1425000	H/O Malignant melanoma
8600	1D18.00	Pain from metastases
13558	1J00.00	Suspected lung cancer
19083	1J04.00	Suspected lymphoma
30715	1J0A.00	Suspected kidney cancer
11541	1J0G.00	Suspected skin cancer
9901	1J0I.00	Suspected breast cancer
32351	44a4.00	Squamous cell carcinoma antigen level
40991	4M2..00	Lymphoma staging system
60918	4M20.00	Lymphoma stage I
94935	4M21.00	Lymphoma stage II
32240	4M22.00	Lymphoma stage III
71672	4M23.00	Lymphoma stage IV
57294	4M3..00	Breslow depth staging for melanoma
101198	4M70.00	Clark melanoma level 1
96280	4M72.00	Clark melanoma level 3
102116	4M73.00	Clark melanoma level 4
48991	5136.00	X-ray metastasis control
67248	5A12.00	Thyroid tumour/metast irradiat
8640	7G03J00	Excision of melanoma
18270	7G03K00	Excision malignant skin tumour
27853	A789500	HIV disease resulting in Kaposi's sarcoma
44617	A789600	HIV disease resulting in Burkitt's lymphoma
66367	A789700	HIV dis resulting oth types of non-Hodgkin's lymphoma
65117	A789900	HIV disease resulting in lymphoid interstitial pneumonitis
51708	A789X00	HIV dis reslt/oth mal neopl/lymph,h'matopoetc+reltd tissu
69767	AyuC600	[X]HIV disease resulting in other non-Hodgkin's lymphoma
14712	B00..00	Malignant neoplasm of lip
9984	B00..11	Carcinoma of lip
61692	B004.00	Malignant neoplasm of lip unspecified, inner aspect
73614	B004000	Malignant neoplasm of lip unspecified, buccal aspect
68399	B004200	Malignant neoplasm of lip unspecified, mucosa
100144	B004300	Malignant neoplasm of lip, oral aspect
16297	B0z0.00	Malignant neoplasm of pharynx unspecified
8386	B11..00	Malignant neoplasm of stomach
10368	B11..11	Gastric neoplasm
14800	B11z.00	Malignant neoplasm of stomach NOS
6806	B12..00	Malignant neoplasm of small intestine and duodenum
43390	B12z.00	Malignant neoplasm of small intestine NOS
1220	B13..00	Malignant neoplasm of colon
101700	B139.00	Hereditary nonpolyposis colon cancer

Medical code	Read Code	Description
28163	B13z.00	Malignant neoplasm of colon NOS
9118	B13z.11	Colonic cancer
35357	B14..00	Malignant neoplasm of rectum, rectosigmoid junction and anus
1800	B141.00	Malignant neoplasm of rectum
7219	B141.11	Carcinoma of rectum
5901	B141.12	Rectal carcinoma
16915	B151.00	Malignant neoplasm of intrahepatic bile ducts
65124	B151000	Malignant neoplasm of interlobular bile ducts
89593	B151200	Malignant neoplasm of intrahepatic biliary passages
58088	B151400	Malignant neoplasm of intrahepatic gall duct
61643	B151z00	Malignant neoplasm of intrahepatic bile ducts NOS
16105	B160.00	Malignant neoplasm of gallbladder
31393	B160.11	Carcinoma gallbladder
8166	B17..00	Malignant neoplasm of pancreas
34388	B17z.00	Malignant neoplasm of pancreas NOS
46613	B18y.00	Malignant neoplasm of specified parts of peritoneum
59388	B18y100	Malignant neoplasm of mesocaecum
30165	B18y200	Malignant neoplasm of mesorectum
50898	B18y300	Malignant neoplasm of omentum
64516	B18y400	Malignant neoplasm of parietal peritoneum
39413	B18y500	Malignant neoplasm of pelvic peritoneum
69821	B18y600	Malignant neoplasm of the pouch of Douglas
90290	B18y700	Malignant neoplasm of mesentery
64106	B18yz00	Malignant neoplasm of specified parts of peritoneum NOS
319	B21..00	Malignant neoplasm of larynx
43111	B213.00	Malignant neoplasm of laryngeal cartilage
63460	B213000	Malignant neoplasm of arytenoid cartilage
37805	B213100	Malignant neoplasm of cricoid cartilage
47862	B213300	Malignant neoplasm of thyroid cartilage
97332	B213z00	Malignant neoplasm of laryngeal cartilage NOS
26813	B21y.00	Malignant neoplasm of larynx, other specified site
9237	B21z.00	Malignant neoplasm of larynx NOS
3903	B22z.00	Malignant neoplasm of bronchus or lung NOS
2587	B22z.11	Lung cancer
95644	B241.00	Malignant neoplasm of heart
63430	B241000	Malignant neoplasm of endocardium
65605	B241200	Malignant neoplasm of myocardium
94975	B241300	Malignant neoplasm of pericardium
101885	B241400	Mesothelioma of pericardium
50289	B241z00	Malignant neoplasm of heart NOS
66750	B24z.00	Malignant neoplasm of heart, thymus and mediastinum NOS
59036	B300.00	Malignant neoplasm of bones of skull and face
53594	B300000	Malignant neoplasm of ethmoid bone
53599	B300100	Malignant neoplasm of frontal bone

Medical code	Read Code	Description
59520	B300200	Malignant neoplasm of malar bone
95458	B300300	Malignant neoplasm of nasal bone
55953	B300400	Malignant neoplasm of occipital bone
50298	B300500	Malignant neoplasm of orbital bone
54747	B300600	Malignant neoplasm of parietal bone
55595	B300700	Malignant neoplasm of sphenoid bone
62104	B300800	Malignant neoplasm of temporal bone
50299	B300900	Malignant neoplasm of zygomatic bone
17475	B300A00	Malignant neoplasm of maxilla
96445	B300B00	Malignant neoplasm of turbinate
44452	B300C00	Malignant neoplasm of vomer
69146	B300z00	Malignant neoplasm of bones of skull and face NOS
71810	B304.00	Malignant neoplasm of scapula and long bones of upper arm
49054	B304000	Malignant neoplasm of scapula
61741	B304200	Malignant neoplasm of humerus
92371	B304300	Malignant neoplasm of radius
64848	B304400	Malignant neoplasm of ulna
65880	B304z00	Malig neop of scapula and long bones of upper arm NOS
73530	B305.00	Malignant neoplasm of hand bones
72464	B305.12	Malignant neoplasm of metacarpal bones
57988	B305000	Malignant neoplasm of carpal bone - scaphoid
69104	B305100	Malignant neoplasm of carpal bone - lunate
94427	B305C00	Malignant neoplasm of fifth metacarpal bone
86812	B305D00	Malignant neoplasm of phalanges of hand
73556	B305z00	Malignant neoplasm of hand bones NOS
54631	B306.00	Malignant neoplasm of pelvic bones, sacrum and coccyx
44609	B306000	Malignant neoplasm of ilium
59223	B306100	Malignant neoplasm of ischium
51921	B306200	Malignant neoplasm of pubis
40966	B306300	Malignant neoplasm of sacral vertebra
66908	B306400	Malignant neoplasm of coccygeal vertebra
50152	B306500	Malignant sacral teratoma
38938	B306z00	Malignant neoplasm of pelvis, sacrum or coccyx NOS
68055	B307.00	Malignant neoplasm of long bones of leg
56513	B307000	Malignant neoplasm of femur
50402	B307100	Malignant neoplasm of fibula
40814	B307200	Malignant neoplasm of tibia
62630	B307z00	Malignant neoplasm of long bones of leg NOS
865	B32..00	Malignant melanoma of skin
70637	B320.00	Malignant melanoma of lip
54632	B321.00	Malignant melanoma of eyelid including canthus
57260	B322.00	Malignant melanoma of ear and external auricular canal
59061	B322000	Malignant melanoma of auricle (ear)
102145	B322100	Malignant melanoma of external auditory meatus

Medical code	Read Code	Description
73744	B322z00	Malignant melanoma of ear and external auricular canal NOS
47252	B323.00	Malignant melanoma of other and unspecified parts of face
41278	B323000	Malignant melanoma of external surface of cheek
71136	B323100	Malignant melanoma of chin
47094	B323200	Malignant melanoma of eyebrow
68133	B323300	Malignant melanoma of forehead
45139	B323400	Malignant melanoma of external surface of nose
58958	B323500	Malignant melanoma of temple
67806	B323z00	Malignant melanoma of face NOS
65625	B324.00	Malignant melanoma of scalp and neck
55881	B324000	Malignant melanoma of scalp
45306	B324100	Malignant melanoma of neck
99257	B324z00	Malignant melanoma of scalp and neck NOS
38689	B325.00	Malignant melanoma of trunk (excluding scrotum)
49814	B325000	Malignant melanoma of axilla
32768	B325100	Malignant melanoma of breast
53629	B325200	Malignant melanoma of buttock
34259	B325300	Malignant melanoma of groin
95629	B325500	Malignant melanoma of perineum
43715	B325600	Malignant melanoma of umbilicus
43463	B325700	Malignant melanoma of back
51209	B325800	Malignant melanoma of chest wall
45760	B325z00	Malignant melanoma of trunk, excluding scrotum, NOS
65164	B326.00	Malignant melanoma of upper limb and shoulder
50505	B326000	Malignant melanoma of shoulder
54685	B326100	Malignant melanoma of upper arm
45755	B326200	Malignant melanoma of fore-arm
62475	B326300	Malignant melanoma of hand
25602	B326400	Malignant melanoma of finger
63997	B326500	Malignant melanoma of thumb
55292	B326z00	Malignant melanoma of upper limb or shoulder NOS
46255	B327.00	Malignant melanoma of lower limb and hip
73536	B327000	Malignant melanoma of hip
51873	B327100	Malignant melanoma of thigh
54305	B327200	Malignant melanoma of knee
39878	B327300	Malignant melanoma of popliteal fossa area
37872	B327400	Malignant melanoma of lower leg
42714	B327500	Malignant melanoma of ankle
61246	B327600	Malignant melanoma of heel
41490	B327700	Malignant melanoma of foot
36899	B327800	Malignant melanoma of toe
53369	B327900	Malignant melanoma of great toe
64327	B327z00	Malignant melanoma of lower limb or hip NOS
42153	B32y.00	Malignant melanoma of other specified skin site

Medical code	Read Code	Description
96585	B32y000	Overlapping malignant melanoma of skin
28556	B32z.00	Malignant melanoma of skin NOS
4632	B33..00	Other malignant neoplasm of skin
37016	B33..14	Malignant neoplasm of sebaceous gland
40443	B33..15	Malignant neoplasm of sweat gland
3445	B33..16	Epithelioma basal cell
18245	B330.00	Malignant neoplasm of skin of lip
53515	B332.00	Malignant neoplasm skin of ear and external auricular canal
33997	B332000	Malignant neoplasm of skin of auricle (ear)
62080	B332100	Malignant neoplasm of skin of external auditory meatus
33271	B332200	Malignant neoplasm of pinna NEC
62399	B332z00	Malig neop skin of ear and external auricular canal NOS
27370	B333.00	Malignant neoplasm skin of other and unspecified parts face
30645	B333000	Malignant neoplasm of skin of cheek, external
49403	B333100	Malignant neoplasm of skin of chin
55670	B333200	Malignant neoplasm of skin of eyebrow
30576	B333300	Malignant neoplasm of skin of forehead
16202	B333400	Malignant neoplasm of skin of nose (external)
21327	B333500	Malignant neoplasm of skin of temple
46008	B333z00	Malignant neoplasm skin other and unspec part of face NOS
54234	B334.00	Malignant neoplasm of scalp and skin of neck
37165	B334000	Malignant neoplasm of scalp
43619	B334100	Malignant neoplasm of skin of neck
73760	B334z00	Malignant neoplasm of scalp or skin of neck NOS
57446	B335.00	Malignant neoplasm of skin of trunk, excluding scrotum
70380	B335000	Malignant neoplasm of skin of axillary fold
37969	B335100	Malignant neoplasm of skin of chest, excluding breast
30543	B335200	Malignant neoplasm of skin of breast
18618	B335300	Malignant neoplasm of skin of abdominal wall
67748	B335400	Malignant neoplasm of skin of umbilicus
66319	B335500	Malignant neoplasm of skin of groin
46458	B335600	Malignant neoplasm of skin of perineum
45077	B335700	Malignant neoplasm of skin of back
62305	B335800	Malignant neoplasm of skin of buttock
23480	B335900	Malignant neoplasm of perianal skin
66447	B335A00	Malignant neoplasm of skin of scapular region
15868	B335z00	Malignant neoplasm of skin of trunk, excluding scrotum, NOS
30747	B336.00	Malignant neoplasm of skin of upper limb and shoulder
43122	B336000	Malignant neoplasm of skin of shoulder
42707	B336100	Malignant neoplasm of skin of upper arm
30577	B336200	Malignant neoplasm of skin of fore-arm
54352	B336300	Malignant neoplasm of skin of hand
25245	B336400	Malignant neoplasm of skin of finger
64406	B336500	Malignant neoplasm of skin of thumb

Medical code	Read Code	Description
60526	B336z00	Malignant neoplasm of skin of upper limb or shoulder NOS
57442	B337.00	Malignant neoplasm of skin of lower limb and hip
70988	B337000	Malignant neoplasm of skin of hip
58601	B337100	Malignant neoplasm of skin of thigh
56954	B337200	Malignant neoplasm of skin of knee
68197	B337300	Malignant neoplasm of skin of popliteal fossa area
33682	B337400	Malignant neoplasm of skin of lower leg
64270	B337500	Malignant neoplasm of skin of ankle
70587	B337700	Malignant neoplasm of skin of foot
65782	B337800	Malignant neoplasm of skin of toe
67914	B337900	Malignant neoplasm of skin of great toe
61194	B337z00	Malignant neoplasm of skin of lower limb or hip NOS
93352	B338.00	Squamous cell carcinoma of skin
2492	B33z.00	Malignant neoplasm of skin NOS
93490	B33z.11	Squamous cell carcinoma of skin NOS
27931	B33z000	Kaposi's sarcoma of skin
15148	B47..00	Malignant neoplasm of testis
38510	B47z.00	Malignant neoplasm of testis NOS
2961	B47z.11	Seminoma of testis
15989	B47z.12	Teratoma of testis
779	B49..00	Malignant neoplasm of urinary bladder
31102	B49z.00	Malignant neoplasm of urinary bladder NOS
1599	B4A0.00	Malignant neoplasm of kidney parenchyma
7978	B4A0000	Hypernephroma
12389	B4A1.00	Malignant neoplasm of renal pelvis
27540	B4A1000	Malignant neoplasm of renal calyces
101608	B4A1100	Malignant neoplasm of ureteropelvic junction
54184	B4A1z00	Malignant neoplasm of renal pelvis NOS
29462	B4Az.00	Malignant neoplasm of kidney or urinary organs NOS
20160	B50..00	Malignant neoplasm of eye
54956	B50z.00	Malignant neoplasm of eye NOS
18617	B51..00	Malignant neoplasm of brain
10851	B51..11	Cerebral tumour - malignant
15711	B510.00	Malignant neoplasm cerebrum (excluding lobes and ventricles)
48073	B510000	Malignant neoplasm of basal ganglia
61399	B510100	Malignant neoplasm of cerebral cortex
99913	B510300	Malignant neoplasm of globus pallidus
70942	B510400	Malignant neoplasm of hypothalamus
62126	B510500	Malignant neoplasm of thalamus
54133	B510z00	Malignant neoplasm of cerebrum NOS
52511	B515.00	Malignant neoplasm of cerebral ventricles
46789	B515000	Malignant neoplasm of choroid plexus
44089	B517.00	Malignant neoplasm of brain stem
64557	B517000	Malignant neoplasm of cerebral peduncle

Medical code	Read Code	Description
49132	B517100	Malignant neoplasm of medulla oblongata
93537	B517200	Malignant neoplasm of midbrain
91240	B517300	Malignant neoplasm of pons
68641	B517z00	Malignant neoplasm of brain stem NOS
41520	B51z.00	Malignant neoplasm of brain NOS
28919	B521.00	Malignant neoplasm of cerebral meninges
70104	B521z00	Malignant neoplasm of cerebral meninges NOS
5637	B53..00	Malignant neoplasm of thyroid gland
9618	B56..00	Secondary and unspecified malignant neoplasm of lymph nodes
7830	B56..11	Lymph node metastases
35053	B57..00	Secondary malig neop of respiratory and digestive systems
6471	B57..11	Metastases of respiratory and/or digestive systems
24301	B57..12	Secondary carcinoma of respiratory and/or digestive systems
4137	B570.00	Secondary malignant neoplasm of lung
64680	B574.00	Secondary malignant neoplasm of small intestine and duodenum
55946	B574000	Secondary malignant neoplasm of duodenum
99511	B574200	Secondary malignant neoplasm of ileum
70026	B574z00	Secondary malig neop of small intestine or duodenum NOS
44529	B575.00	Secondary malignant neoplasm of large intestine and rectum
28727	B575000	Secondary malignant neoplasm of colon
62909	B575100	Secondary malignant neoplasm of rectum
36200	B575z00	Secondary malig neop of large intestine or rectum NOS
15103	B577.00	Secondary malignant neoplasm of liver
4403	B577.11	Liver metastases
1952	B580.00	Secondary malignant neoplasm of kidney
19945	B582.00	Secondary malignant neoplasm of skin
43930	B582000	Secondary malignant neoplasm of skin of head
100296	B582100	Secondary malignant neoplasm of skin of face
35999	B582200	Secondary malignant neoplasm of skin of neck
41144	B582300	Secondary malignant neoplasm of skin of trunk
63896	B582400	Secondary malignant neoplasm of skin of shoulder and arm
48828	B582500	Secondary malignant neoplasm of skin of hip and leg
9505	B582600	Secondary malignant neoplasm of skin of breast
55096	B582z00	Secondary malignant neoplasm of skin NOS
33843	B583.00	Secondary malignant neoplasm of brain and spinal cord
5198	B583000	Secondary malignant neoplasm of brain
38918	B583100	Secondary malignant neoplasm of spinal cord
5199	B583200	Cerebral metastasis
59375	B583z00	Secondary malignant neoplasm of brain or spinal cord NOS
18616	B58y.00	Secondary malignant neoplasm of other specified sites
16760	B58y000	Secondary malignant neoplasm of breast
55090	B58y100	Secondary malignant neoplasm of uterus
73616	B58y200	Secondary malignant neoplasm of cervix uteri
97832	B58y211	Secondary cancer of the cervix

Medical code	Read Code	Description
70736	B58y300	Secondary malignant neoplasm of vagina
60335	B58y400	Secondary malignant neoplasm of vulva
65490	B58y411	Secondary cancer of the vulva
21590	B58y500	Secondary malignant neoplasm of prostate
34145	B58y600	Secondary malignant neoplasm of testis
49145	B58y700	Secondary malignant neoplasm of penis
45824	B58y900	Secondary malignant neoplasm of tongue
22524	B58yz00	Secondary malignant neoplasm of other specified site NOS
21402	B602.00	Burkitt's lymphoma
59115	B602100	Burkitt's lymphoma of lymph nodes of head, face and neck
100006	B602200	Burkitt's lymphoma of intrathoracic lymph nodes
97577	B602300	Burkitt's lymphoma of intra-abdominal lymph nodes
92380	B602500	Burkitt's lymphoma of lymph nodes of inguinal region and leg
71304	B602z00	Burkitt's lymphoma NOS
5179	B620.00	Nodular lymphoma (Brill - Symmers disease)
66327	B620000	Nodular lymphoma of unspecified site
45264	B620100	Nodular lymphoma of lymph nodes of head, face and neck
92068	B620300	Nodular lymphoma of intra-abdominal lymph nodes
94995	B620500	Nodular lymphoma of lymph nodes of inguinal region and leg
58082	B620800	Nodular lymphoma of lymph nodes of multiple sites
65701	B620z00	Nodular lymphoma NOS
3604	B627.00	Non - Hodgkin's lymphoma
28639	B627000	Follicular non-Hodgkin's small cleaved cell lymphoma
70842	B627100	Follicular non-Hodg mixed sml cleavd & lge cell lymphoma
49262	B627200	Follicular non-Hodgkin's large cell lymphoma
50668	B627300	Diffuse non-Hodgkin's small cell (diffuse) lymphoma
50695	B627500	Diffuse non-Hodgkin mixed sml & lge cell (diffuse) lymphoma
53551	B627600	Diffuse non-Hodgkin's immunoblastic (diffuse) lymphoma
17460	B627700	Diffuse non-Hodgkin's lymphoblastic (diffuse) lymphoma
65180	B627800	Diffuse non-Hodgkin's lymphoma undifferentiated (diffuse)
95715	B627900	Mucosa-associated lymphoma
95545	B627911	Maltoma
101114	B627A00	Diffuse non-Hodgkin's large cell lymphoma
31576	B627B00	Other types of follicular non-Hodgkin's lymphoma
21549	B627C00	Follicular non-Hodgkin's lymphoma
17182	B627C11	Follicular lymphoma NOS
70509	B627D00	Diffuse non-Hodgkin's centroblastic lymphoma
102594	B627E00	Diffuse large B-cell lymphoma
31794	B627W00	Unspecified B-cell non-Hodgkin's lymphoma
39798	B627X00	Diffuse non-Hodgkin's lymphoma, unspecified
17887	B62x.00	Malignant lymphoma otherwise specified
90201	B62x000	T-zone lymphoma
57737	B62x100	Lymphoepithelioid lymphoma
12464	B62x200	Peripheral T-cell lymphoma

Medical code	Read Code	Description
62437	B62x400	Malignant reticulosis
58962	B62x500	Malignant immunoproliferative small intestinal disease
95630	B62x600	True histiocytic lymphoma
44318	B62xX00	Oth and unspecif peripheral & cutaneous T-cell lymphomas
12335	B62y.00	Malignant lymphoma NOS
57427	B62y000	Malignant lymphoma NOS of unspecified site
50696	B62y100	Malignant lymphoma NOS of lymph nodes of head, face and neck
72725	B62y200	Malignant lymphoma NOS of intrathoracic lymph nodes
42579	B62y300	Malignant lymphoma NOS of intra-abdominal lymph nodes
34089	B62y400	Malignant lymphoma NOS of lymph nodes of axilla and arm
63105	B62y500	Malignant lymphoma NOS of lymph node inguinal region and leg
71262	B62y600	Malignant lymphoma NOS of intrapelvic lymph nodes
60092	B62y700	Malignant lymphoma NOS of spleen
15504	B62y800	Malignant lymphoma NOS of lymph nodes of multiple sites
15027	B62yz00	Malignant lymphoma NOS
19372	B64..00	Lymphoid leukaemia
4222	B64..11	Lymphatic leukaemia
4251	B640.00	Acute lymphoid leukaemia
8625	B641.00	Chronic lymphoid leukaemia
27790	B641.11	Chronic lymphatic leukaemia
72774	B642.00	Subacute lymphoid leukaemia
49725	B64y.00	Other lymphoid leukaemia
31586	B64y100	Prolymphocytic leukaemia
37461	B64y200	Adult T-cell leukaemia
38331	B64yz00	Other lymphoid leukaemia NOS
38914	B64z.00	Lymphoid leukaemia NOS
55675	B717011	Endocrine tumour of pancreas
2610	B7G..11	Adenoma of thyroid gland
19686	B828.00	Melanoma in situ of skin
46536	B828000	Melanoma in situ of lip
37108	B828100	Melanoma in situ of eyelid, including canthus
72032	B828200	Melanoma in situ of ear and external auricular canal
97858	B828300	Melanoma in situ of scalp and neck
59768	B828400	Melanoma in situ of trunk
56694	B828500	Melanoma in situ of upper limb, including shoulder
47850	B828600	Melanoma in situ of lower limb, including hip
49572	B828700	Melanoma in situ of scalp
52332	B828800	Melanoma in situ of back of hand
71044	B828900	Melanoma in situ of back
54246	B828W00	Melanoma in situ, unspecified
61989	B828X00	Melanoma in situ of other and unspecified parts of face
25961	BB17.00	[M]Large cell carcinoma NOS
48048	BB1B.00	[M]Giant cell and spindle cell carcinoma
35474	BB1C.00	[M]Giant cell carcinoma

Medical code	Read Code	Description
6966	BB1D.00	[M]Spindle cell carcinoma
69300	BB1F.00	[M]Polygonal cell carcinoma
61984	BB1G.00	[M]Spheroidal cell carcinoma
9291	BB1J.00	[M]Small cell carcinoma NOS
66541	BB1J.12	[M]Round cell carcinoma
9156	BB1K.00	[M]Oat cell carcinoma
67970	BB1L.00	[M]Small cell carcinoma, fusiform cell type
30988	BB1M.00	[M]Small cell carcinoma, intermediate cell
21217	BB1N.00	[M]Small cell-large cell carcinoma
34395	BB24.00	[M]Verrucous carcinoma NOS
43717	BB24.11	[M]Verrucous epidermoid carcinoma
4852	BB24.12	[M]Verrucous squamous cell carcinoma
20807	BB26.00	[M]Papillary squamous cell carcinoma
67912	BB26.11	[M]Papillary epidermoid carcinoma
10134	BB29.00	[M]Squamous cell carcinoma in situ NOS
48182	BB29.11	[M]Epidermoid carcinoma in situ
19041	BB29.12	[M]Intraepidermal carcinoma NOS
19678	BB29.13	[M]Intraepithelial squamous cell carcinoma
1624	BB2A.00	[M]Squamous cell carcinoma NOS
56600	BB2A.11	[M]Epidermoid carcinoma NOS
57680	BB2A.12	[M]Spinous cell carcinoma
94873	BB2A.13	[M]Squamous cell carcinoma of skin NOS
24293	BB2B.00	[M]Squamous cell carcinoma, metastatic NOS
29787	BB2C.00	[M]Squamous cell carcinoma, keratinising type NOS
57513	BB2C.11	[M]Epidermoid carcinoma, keratinising type
59143	BB2D.00	[M]Squamous cell carcinoma, large cell, non-keratinising
41816	BB2E.00	[M]Squamous cell carcinoma, small cell, non-keratinising
45458	BB2F.00	[M]Squamous cell carcinoma, spindle cell type
31004	BB2G.00	[M]Adenoid squamous cell carcinoma
33497	BB2J.00	[M]Squamous cell carcinoma, microinvasive
21652	BB42.00	[M]Transitional cell carcinoma in situ
6436	BB43.00	[M]Transitional cell carcinoma NOS
12388	BB43.11	[M]Urothelial carcinoma
58798	BB47.00	[M]Transitional cell carcinoma, spindle cell type
9712	BB4A.00	[M]Papillary transitional cell carcinoma
8032	BB5B.00	[M]Pancreatic adenomas and carcinomas
65658	BB5B000	[M]Islet cell adenoma
11469	BB5B011	[M]Nesidioblastoma
63102	BB5B100	[M]Islet cell carcinoma
9224	BB5B200	[M]Insulinoma NOS
95609	BB5B300	[M]Insulinoma, malignant
58022	BB5B400	[M]Glucagonoma NOS
32294	BB5B500	[M]Glucagonoma, malignant
98825	BB5B600	[M]Mixed islet cell and exocrine adenocarcinoma

Medical code	Read Code	Description
21659	BB5Bz00	[M]Pancreatic adenoma or carcinoma NOS
36031	BB5D.00	[M]Hepatobiliary tract adenomas and carcinomas
70516	BB5D.11	[M]Biliary tract adenomas and adenocarcinomas
17979	BB5D011	[M]Cholangioma
8711	BB5D100	[M]Cholangiocarcinoma
40438	BB5D111	[M]Bile duct carcinoma
30596	BB5D200	[M]Bile duct cystadenoma
41313	BB5D300	[M]Bile duct cystadenocarcinoma
40240	BB5D500	[M]Hepatocellular carcinoma NOS
20234	BB5D511	[M]Hepatoma NOS
26814	BB5D512	[M]Hepatoma, malignant
25641	BB5D513	[M]Liver cell carcinoma
46771	BB5D800	[M]Hepatocellular carcinoma, fibrolamellar
53987	BB5Dz00	[M]Hepatobiliary adenoma or carcinoma NOS
3923	BB5R.00	[M]Carcinoid tumours
38444	BB5R000	[M]Carcinoid tumour NOS
34110	BB5R100	[M]Carcinoid tumour, malignant
23081	BB5R111	[M]Carcinoid bronchial adenoma
39130	BB5R200	[M]Carcinoid tumour, argentaffin, NOS
49797	BB5R211	[M]Argentaffinoma NOS
99296	BB5R400	[M]Carcinoid tumour, nonargentaffin, NOS
100625	BB5R500	[M]Carcinoid tumour, nonargentaffin, malignant
55468	BB5R600	[M]Mucocarcinoid tumour, malignant
69210	BB5R611	[M]Goblet cell tumour
56794	BB5R800	[M]Adenocarcinoid tumour
26253	BB5R900	[M]Neuroendocrine carcinoma
32641	BB5RA00	[M]Merkel cell carcinoma
45573	BB5Rz00	[M]Carcinoid tumours NOS
26848	BB5S.00	[M]Respiratory tract adenomas and adenocarcinomas
34015	BB5S200	[M]Bronchiolo-alveolar adenocarcinoma
36530	BB5S211	[M]Alveolar cell carcinoma
16723	BB5S212	[M]Bronchiolar carcinoma
57802	BB5S400	[M]Alveolar adenocarcinoma
36221	BB5Sz00	[M]Respiratory tract adenoma or adenocarcinoma NOS
26120	BB5V.00	[M]Pituitary adenomas and carcinomas
68456	BB5V100	[M]Chromophobe carcinoma
36876	BB5V311	[M]Eosinophil carcinoma
72277	BB5V700	[M]Basophil carcinoma
40622	BB5V711	[M]Mucoid cell carcinoma
57422	BB5Vz00	[M]Pituitary adenoma or carcinoma NOS
62199	BB5W.00	[M]Oxyphilic adenomas and adenocarcinomas
71497	BB5W100	[M]Oxyphilic adenocarcinoma
29008	BB5W111	[M]Hurthle cell adenocarcinoma
53129	BB5W112	[M]Oncytic adenocarcinoma

Medical code	Read Code	Description
73662	BB5Wz00	[M]Oxyphilic adenoma or adenocarcinoma NOS
36882	BB5X.00	[M]Clear cell adenomas and adenocarcinomas
37354	BB5X100	[M]Clear cell adenocarcinoma NOS
72192	BB5Xz00	[M]Clear cell adenoma or adenocarcinoma NOS
8101	BB5a.00	[M]Renal adenoma and carcinoma
10668	BB5a000	[M]Renal cell carcinoma
52266	BB5a011	[M]Grawitz tumour
15419	BB5a012	[M]Hypernephroma
35467	BB5az00	[M]Renal adenoma or carcinoma NOS
34096	BB5b.00	[M]Granular cell carcinoma
4217	BB5c.00	[M]Parathyroid adenomas and adenocarcinomas
42169	BB5cz00	[M]Parathyroid adenoma or adenocarcinoma NOS
39038	BB85.00	[M]Signet ring carcinoma
61588	BB85000	[M]Signet ring cell carcinoma
54874	BB85100	[M]Metastatic signet ring cell carcinoma
53694	BB85111	[M]Krukenberg tumour
94438	BB85z00	[M]Signet ring carcinoma NOS
40359	BB94.00	[M]Juvenile breast carcinoma
67701	BB94.11	[M]Secretory breast carcinoma
16677	BB9B.00	[M]Medullary carcinoma NOS
47920	BB9B.11	[M]C cell carcinoma
42542	BB9K.00	[M]Paget's disease and infiltrating breast duct carcinoma
12480	BB9K000	[M]Paget's disease and intraductal carcinoma of breast
3710	BBB1.00	[M]Adenolymphoma
59787	BBC9.00	[M]Tubular androblastoma NOS
38979	BBC9.13	[M]Sertoli cell tumour
29580	BBCA.00	[M]Sertoli cell carcinoma
7693	BBE..00	[M]Naevi and melanomas
579	BBE1.00	[M]Malignant melanoma NOS
24551	BBE1.11	[M]Melanocarcinoma
7483	BBE1.12	[M]Melanoma NOS
44157	BBE1.13	[M]Melanosarcoma NOS
67966	BBE1.14	[M]Naevocarcinoma
51353	BBE1000	[M]Malignant melanoma, regressing
58835	BBE1100	[M]Desmoplastic melanoma, malignant
20982	BBE2.00	[M]Nodular melanoma
68889	BBE4.00	[M]Balloon cell melanoma
17232	BBEA.00	[M]Amelanotic melanoma
63574	BBEC.00	[M]Malignant melanoma in junctional naevus
62088	BBEG.00	[M]Malignant melanoma in Hutchinson's melanotic freckle
11922	BBEG.11	[M]Lentigo maligna melanoma
22692	BBEG000	[M]Acral lentiginous melanoma, malignant
24208	BBEH.00	[M]Superficial spreading melanoma
73251	BBEM.00	[M]Malignant melanoma in giant pigmented naevus

Medical code	Read Code	Description
1261	BBEN.00	[M]Epithelioid and spindle cell naevus
4871	BBEN.11	[M]Juvenila melanoma
23085	BBEP.00	[M]Epithelioid cell melanoma
44061	BBEQ.00	[M]Spindle cell melanoma NOS
92293	BBES.00	[M]Spindle cell melanoma, type B
40303	BBET.00	[M]Mixed epithelioid and spindle melanoma
39059	BBEX.00	[M]Melanoma in situ
33734	BBEz.00	[M]Naevi or melanoma NOS
17178	BBg..00	[M]Lymphomas, NOS or diffuse
49131	BBg0.00	[M]Lymphomatous tumour, benign
36114	BBg1.00	[M]Malignant lymphoma NOS
1483	BBg1.11	[M]Lymphoma NOS
23711	BBg1000	[M]Malignant lymphoma, diffuse NOS
16460	BBg2.00	[M]Malignant lymphoma, non Hodgkin's type
3371	BBg2.11	[M]Non Hodgkins lymphoma
71117	BBg3.00	[M]Malignant lymphoma, undifferentiated cell type NOS
46931	BBg4.00	[M]Malignant lymphoma, stem cell type
69301	BBg5.00	[M]Malignant lymphoma, convoluted cell type NOS
41754	BBg7.00	[M]Malignant lymphoma, lymphoplasmacytoid type
48253	BBg8.00	[M]Malignant lymphoma, immunoblastic type
68964	BBgA.00	[M]Malignant lymphoma, centroblastic-centrocytic, diffuse
41841	BBgB.00	[M]Malignant lymphoma, follicular centre cell NOS
69980	BBgC.00	[M]Malignant lymphoma, lymphocytic, well differentiated NOS
21463	BBgC.11	[M]Lymphocytic lymphoma NOS
60504	BBgC.12	[M]Lymphocytic lymphosarcoma NOS
51852	BBgD.00	[M]Malig lymphoma, lymphocytic, intermediate different NOS
39906	BBgE.00	[M]Malignant lymphoma, centrocytic
72196	BBgG.00	[M]Malignant lymphoma, lymphocytic, poorly different NOS
67203	BBgG.11	[M]Lymphoblastic lymphosarcoma NOS
34352	BBgG.12	[M]Lymphoblastic lymphoma NOS
52591	BBgG.13	[M]Lymphoblastoma NOS
60275	BBgJ.00	[M]Malignant lymphoma, centroblastic type NOS
66603	BBgK.00	[M]Malig lymphoma, follicular centre cell, non-cleaved NOS
46877	BBgL.00	[M]Malignant lymphoma, small lymphocytic NOS
31726	BBgM.00	[M]Malignant lymphoma, small cleaved cell, diffuse
61251	BBgN.00	[M]Malign lymphoma,lymphocytic,intermediate differn, diffuse
71652	BBgP.00	[M]Malignant lymphoma, mixed small and large cell, diffuse
58015	BBgQ.00	[M]Malignant lymphomatous polyposis
33869	BBgR.00	[M]Malignant lymphoma, large cell, diffuse NOS
63994	BBgS.00	[M]Malignant lymphoma, large cell, cleaved, diffuse
71619	BBgT.00	[M]Malignant lymphoma, large cell, noncleaved, diffuse
51680	BBgV.00	[M]Malignant lymphoma, small cell, noncleaved, diffuse
51895	BBgz.00	[M]Lymphoma, diffuse or NOS
20437	BBk..00	[M]Lymphomas, nodular or follicular

Medical code	Read Code	Description
63699	BBk0.00	[M]Malignant lymphoma, nodular NOS
64947	BBk0.11	[M]Brill - Symmers' disease
27562	BBk0.12	[M]Follicular lymphosarcoma NOS
49253	BBk0.13	[M]Giant follicular lymphoma
98961	BBk2.00	[M]Malignant lymphoma, centroblastic-centrocytic, follicular
97852	BBk7.00	[M]Malignant lymphoma, centroblastic type, follicular
40513	BBkz.00	[M]Lymphoma, nodular or follicular NOS
57544	BBm4.00	[M]True histiocytic lymphoma
40766	BBm5.00	[M] Peripheral T-cell lymphoma NOS
31492	BBm9.00	[M] Monocytoid B-cell lymphoma
16774	BBmD.00	[M] Cutaneous lymphoma
18383	BBmH.00	[M] Large cell lymphoma
48155	BBr2.00	[M]Lymphoid leukaemias
12146	BBr2000	[M]Lymphoid leukaemia NOS
20635	BBr2011	[M]Lymphatic leukaemia
37410	BBr2100	[M]Acute lymphoid leukaemia
41500	BBr2300	[M]Chronic lymphoid leukaemia
46048	BBr2500	[M]Prolymphocytic leukaemia
50928	BBr2600	[M]Burkitt's cell leukaemia
29335	BBr2700	[M]Adult T-cell leukaemia/lymphoma
31749	BBv0.00	[M]Monocytoid B-cell lymphoma
27965	BBv2.00	[M]AngiocentricT-cell lymphoma
19144	Byu4.00	[X]Melanoma and other malignant neoplasms of skin
56925	Byu4000	[X]Malignant melanoma of other+unspecified parts of face
19444	Byu4100	[X]Malignant melanoma of skin, unspecified
57184	Byu4200	[X]Oth malignant neoplasm/skin of oth+unspecfd parts of face
56121	Byu4300	[X]Malignant neoplasm of skin, unspecified
12499	Byu6.00	[X]Malignant neoplasm of breast
40608	ByuB.00	[X]Malignant neoplasm of thyroid and other endocrine glands
64309	ByuB100	[X]Malignant neoplasm of endocrine gland, unspecified
40740	ByuD.00	[X]Malignant neoplasms of lymphoid, haematopoietic and rela
43415	ByuD000	[X]Other Hodgkin's disease
67518	ByuD100	[X]Other types of follicular non-Hodgkin's lymphoma
98596	ByuD200	[X]Other types of diffuse non-Hodgkin's lymphoma
64336	ByuD300	[X]Other specified types of non-Hodgkin's lymphoma
67029	ByuD500	[X]Other lymphoid leukaemia
61693	ByuD600	[X]Other myeloid leukaemia
89762	ByuD700	[X]Other monocytic leukaemia
89329	ByuD800	[X]Other specified leukaemias
65165	ByuD900	[X]Other leukaemia of unspecified cell type
72500	ByuDB00	[X]Mal neoplasm/lymphoid,haematopoietic+related tissu,unspcf
64515	ByuDC00	[X]Diffuse non-Hodgkin's lymphoma, unspecified
63375	ByuDE00	[X]Unspecified B-cell non-Hodgkin's lymphoma
8649	ByuDF00	[X]Non-Hodgkin's lymphoma, unspecified type

Medical code	Read Code	Description
7940	ByuDF11	[X]Non-Hodgkin's lymphoma NOS
101772	ByuF.00	[X]In situ neoplasms
12106	ZV10.00	[V]Personal history of malignant neoplasm
62814	ZV10000	[V]Personal history of malig neop of gastrointestinal tract
68018	ZV10011	[V]Personal history of malignant neoplasm of anus
64568	ZV10012	[V]Personal history of malig neop of gastrointestinal tract
57727	ZV10014	[V]Personal history of malignant neoplasm of large intestine
58177	ZV10015	[V]Personal history of malignant neoplasm of liver
51001	ZV10016	[V]Personal history of malignant neoplasm of oesophagus
62785	ZV10017	[V]Personal history of malignant neoplasm of rectum
49447	ZV10018	[V]Personal history of malignant neoplasm of stomach
99931	ZV10019	[V]Personal history of malignant neoplasm of tongue
49289	ZV10100	[V]Personal history of malig neop of trachea/bronchus/lung
32246	ZV10111	[V]Personal history of malignant neoplasm of bronchus
29284	ZV10112	[V]Personal history of malignant neoplasm of lung
72262	ZV10200	[V]Personal history of malig neop other intrathoracic organ
61655	ZV10211	[V]Personal history of malignant neoplasm - accessory sinus
43311	ZV10212	[V]Personal history of malignant neoplasm of larynx
39863	ZV10214	[V]Personal history of malignant neoplasm of nose
16639	ZV10300	[V]Personal history of malignant neoplasm of breast
9444	ZV10400	[V]Personal history of malignant neoplasm of genital organ
23936	ZV10411	[V]Personal history of malignant neoplasm of cervix uteri
52141	ZV10414	[V]Personal history of malignant neoplasm of ovary
37306	ZV10415	[V]Personal history of malignant neoplasm of prostate
48808	ZV10416	[V]Personal history of malignant neoplasm of testis
46779	ZV10417	[V]Personal history of malignant neoplasm of uterine body
30322	ZV10500	[V]Personal history of malignant neoplasm of urinary organ
35816	ZV10511	[V]Personal history of malignant neoplasm of bladder
47683	ZV10512	[V]Personal history of malignant neoplasm of kidney
28881	ZV10513	[V]Personal history of malignant neoplasm of kidney
36693	ZV10600	[V]Personal history of leukaemia
94597	ZV10611	[V]Personal history of lymphoid leukaemia
72204	ZV10700	[V]Personal history other lymphatic/haematopoietic neoplasm
40561	ZV10711	[V]Personal history of Hodgkin's disease
66457	ZV10y00	[V]Personal history of other specified malignant neoplasm
46282	ZV10y11	[V]Personal history of malignant neoplasm of bone
48085	ZV10y12	[V]Personal history of malignant neoplasm of brain
47669	ZV10y14	[V]Personal history of malignant neoplasm of skin
35771	ZV10y15	[V]Personal history of malignant neoplasm of thyroid
45803	ZV10y16	[V]Personal history of malignant neoplasm of tongue
68612	ZV10z00	[V]Personal history of unspecified malignant neoplasm
12079	ZV16.00	[V]Family history of malignant neoplasm
43864	ZV16000	[V]Family history of malig neop of gastrointestinal tract
22519	ZV16100	[V]Family history of malig neop of trachea/bronchus/lung

Medical code	Read Code	Description
55907	ZV16111	[V]Family history of malignant neoplasm of bronchus
13273	ZV16112	[V]Family history of malignant neoplasm of lung
69337	ZV16113	[V]Family history of malignant neoplasm of trachea
50028	ZV16200	[V]Family history malig neop other respiratory/intrathor org
94022	ZV16211	[V]Family history malignant neoplasm other respiratory organ
16786	ZV16300	[V]Family history of malignant neoplasm of breast
22624	ZV16400	[V]Family history of malignant neoplasm of genital organ
42099	ZV16500	[V]Family history of malignant neoplasm of urinary organ
26622	ZV16600	[V]Family history of leukaemia
56330	ZV16700	[V]Family history of other lymphatic/haematopoietic neoplasm
46666	ZV16711	[V]Family history of other lymphatic neoplasm
25821	ZV16y00	[V]Family history of other malignant neoplasm
25655	ZV16z00	[V]Family history of unspecified malignant neoplasm
10439	ZV76.00	[V]Screening for malignant neoplasm
99189	ZV76000	[V]Screening for malignant neoplasm of respiratory organ
4862	ZV76100	[V]Screening for malignant neoplasm of breast
25835	ZV76200	[V]Screening for malignant neoplasm of cervix

3. AMENDMENT

This protocol has been amended for the following reason.
For the primary analyses, we initially planned to use the information from the GP questionnaires (a subpopulation of identified subjects from CPRD-HES).
However, based on information obtained from the GPs, transplant rejection events appeared to be under-reported and under-documented by GPs. Therefore, HES was used as primary source of information to carry out the primary analyses and combined information from HES / CPRD and questionnaires was used to carry out analyses for the secondary analyses.

3.1. Amendment 1

The original approved protocol text is indicated in "*italics*" and the amended text is indicated in "normal" font below:

Contributing authors

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1. *GlaxoSmithKline Biologicals, Central Epidemiology (a), GlaxoSmithKline , Worldwide Epidemiology, Observational Data Analytics (b), GlaxoSmithKline Biologicals Clinical Safety and Pharmacovigilance (c).*
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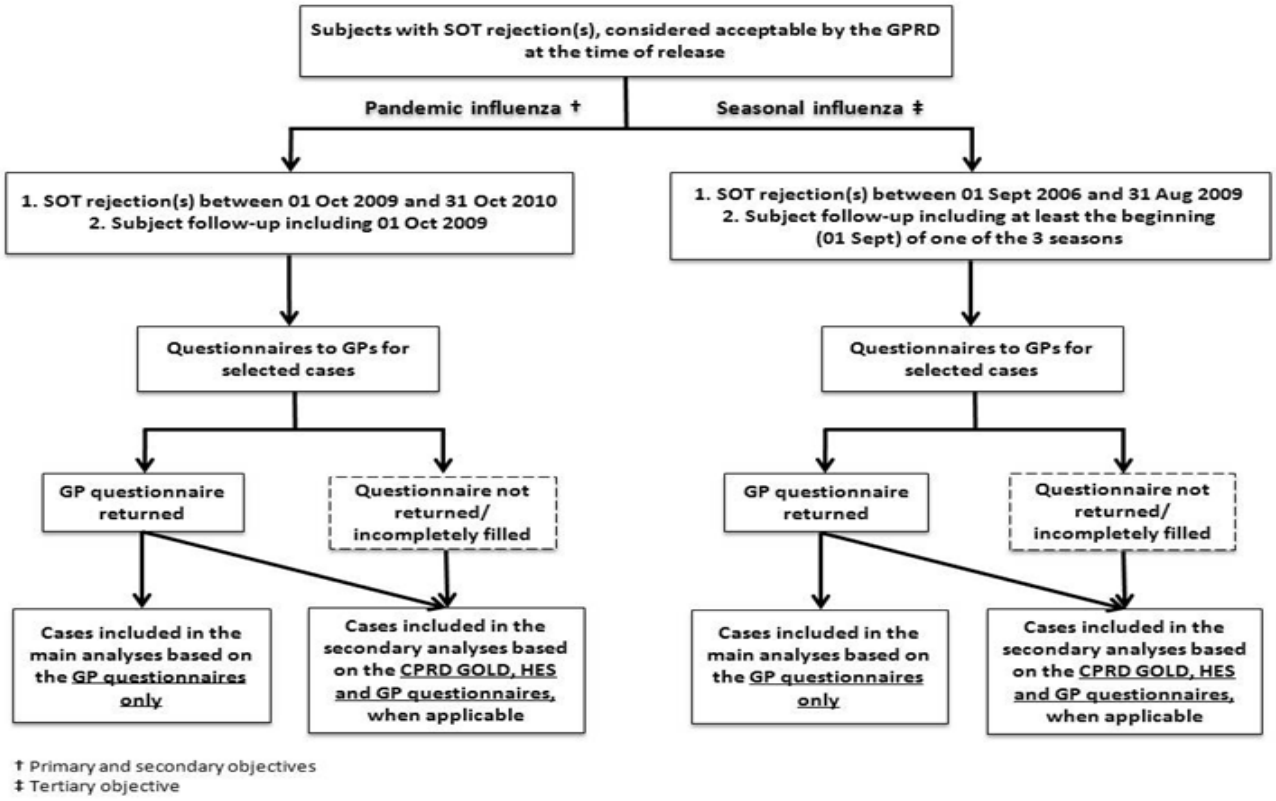
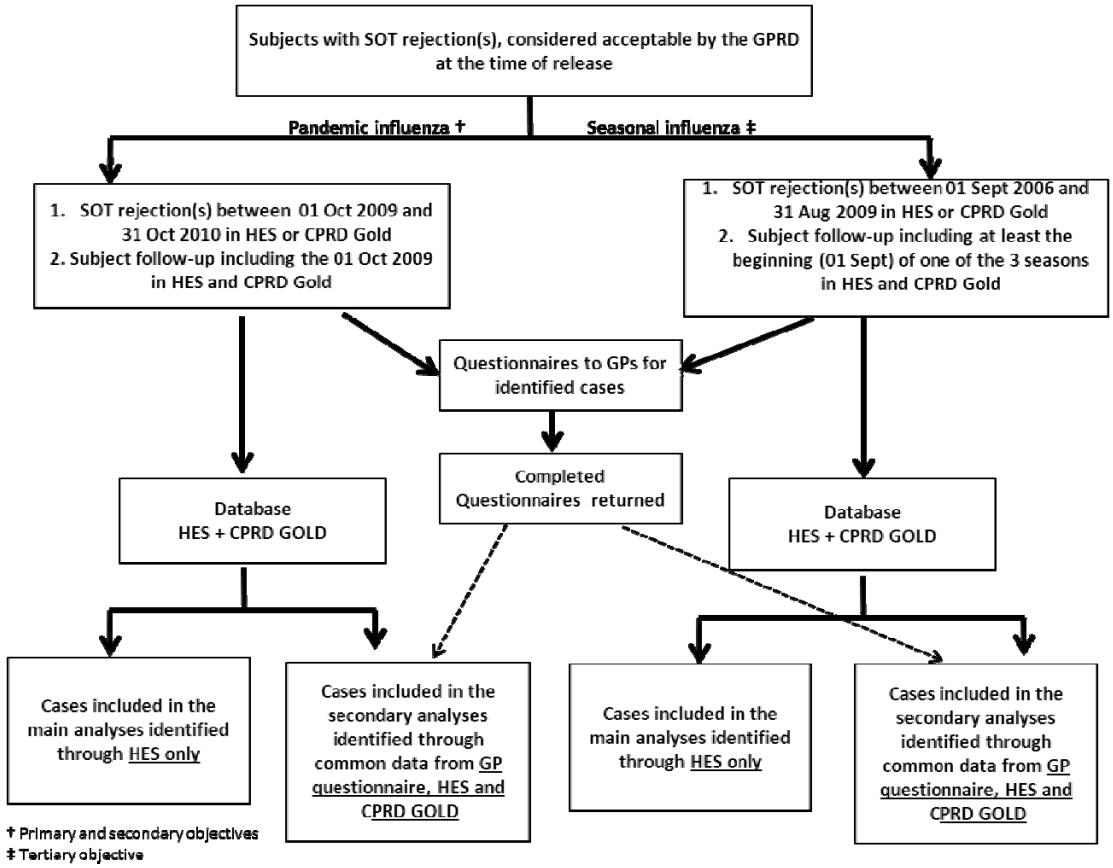
1. GlaxoSmithKline Biologicals, Central Epidemiology (a), GlaxoSmithKline , Worldwide Epidemiology, Observational Data Analytics (b), GlaxoSmithKline Vaccine Clinical Safety and Pharmacovigilance (c).

Figure 1 Identification of the study population

Initial figure from the approved protocol:



Amended figure 1: Identification of the study population



Data collection

The final study database will consist of data extracted from the CPRD GOLD and HES, and additional data obtained from complementary information provided by the GPs using a standardised questionnaire (see Appendix B). Subject data necessary for analysis and reporting will be entered into a validated database or data system and a study-specific dataset will be created. Data management will be performed in accordance with applicable GSK standards. No monitoring will be performed. The study database will be archived by GSK Biologicals' Data Management.

The final study database will consist of data extracted from the CPRD GOLD and HES, and additional data obtained from complementary information provided by the GPs using a standardised questionnaire (see Appendix B). Subject data necessary for analysis and reporting will be entered into a validated database or data system and a study-specific dataset will be created.
Data management will be performed in accordance with applicable GSK standards. The study database will be archived by GSK Biologicals' Data Management.
For the GP questionnaires, as no queries can be sent to GPs to further clarify uncertain information for a specific field, data implying interpretation (e.g., two dates for the same event, unreadable information) will be coded as missing for the purpose of analysis.

Statistical methods – 1) Subject's follow-up

For each subject, the follow-up will be defined separately for each season. The beginning of the follow-up will be 01 October 2009 for the pandemic season, and 01 September of each season for the other influenza seasons (i.e., 2006/2007, 2007/2008, 2008/2009). The end of follow-up will correspond to whichever of the following dates/events comes first:

- *31 October 2010 for the pandemic study period; 31 August 2007, 2008, or 2009 for the seasonal influenza study periods;*
- *A new transplantation event as defined in Appendix A;*
- *Subject's death;*
- *Last collection date of the GP practice the subject is registered with;*
- *Transfer out date of the subject: the subject will be included up to the "transfer out date", in order to ensure continuous follow-up during a given season.*

For each subject, the follow-up will be defined separately for each season. The beginning of the follow-up will be 01 October 2009 for the pandemic season, and 01 September of each season for the other influenza seasons (i.e., 2006/2007, 2007/2008, 2008/2009). The end of follow-up will correspond to whichever of the following dates/events comes first:

- 31 October 2010 for the pandemic study period; 31 August 2007, 2008, or 2009 for the seasonal influenza study periods;
- A new transplantation event as defined in Appendix A;
- Subject's death;
- Last collection date of the GP practice the subject is registered with;
- Transfer out date of the subject: the subject will be included up to the "transfer out date", in order to ensure continuous follow-up during a given season.
- Last date of collection of HES data in the CPRD-GOLD release used for the analyses.

For the analyses of the pooled seasons, the separate seasonal follow-ups will be pooled.

Statistical methods – 2) Subsets of the study population

Four subsets of cases will be defined for the analyses.

Pandemic influenza study period (01 October 2009 – 31 October 2010):

- *Subset 1a. The primary pandemic influenza subset will include subjects:*
  - *with a follow-up during the pandemic season including 01 October 2009, and*
  - *with at least one rejection reported in the GP questionnaire, within the subject's follow-up for the pandemic season.*
- *Subset 1b. The secondary pandemic influenza subset will include:*
  - *subjects from Subset 1a, and*
  - *additional subjects from the CPRD GOLD:*
    - *for whom the GP questionnaire was not returned;*
    - *with rejection(s) reported in the CPRD GOLD and/or HES between 01 October 2009 and 31 October 2010;*
    - *with a follow-up during the pandemic season including 01 October 2009.*

Seasonal influenza study period (01 September 2006 – 31 August 2009):

- *Subset 2a. The primary seasonal influenza subset will include subjects with a follow-up during at least one of the influenza seasons (2006/2007, 2007/2008 or 2008/2009). The subject's follow-up must include:*
  - *01 September, and*
  - *at least one rejection reported in the GP questionnaire in at least one of the 3 influenza seasons.*
- *Subset 2b. The secondary seasonal influenza subset will include:*
  - *subjects from Subset 2a, and*
  - *additional subjects from the CPRD GOLD:*
    - *for whom the GP questionnaire was not returned;*
    - *with rejection(s) reported in the CPRD GOLD and/or HES between 01 September 2006 and 31 August 2009;*
    - *with a follow-up including 01 September in at least one season in which a rejection occurred.*

Four subsets of cases will be defined for the analyses (see figure 3).

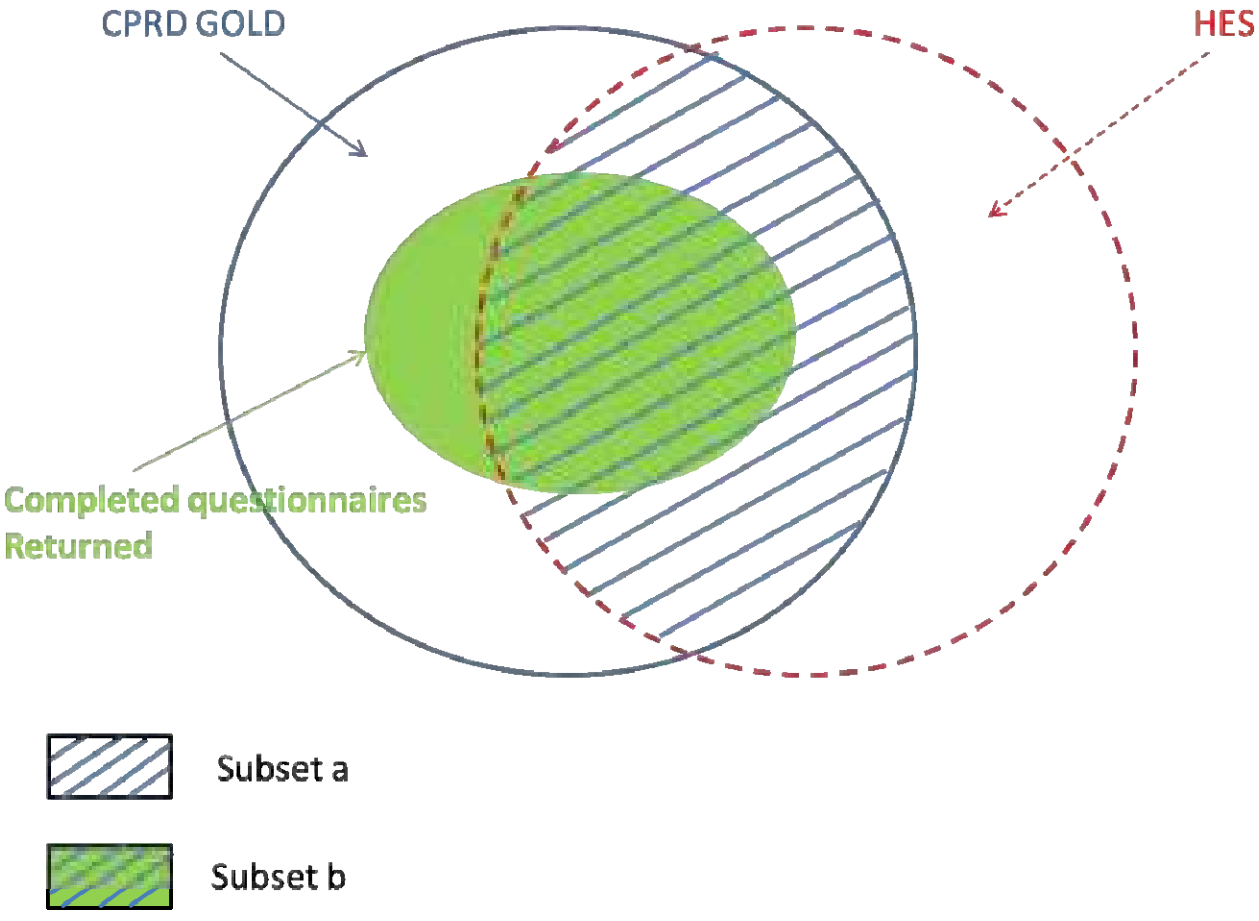
Pandemic influenza study period (01 October 2009 – 31 October 2010):

- Subset 1a. The primary pandemic influenza subset will include subjects:
  - with a follow-up in the CPRD GOLD and in HES during the pandemic season including 01 October 2009 and the preceding 180 days period (from 04 April 2009) ,
    AND
  - with at least one rejection reported in HES, within the subject's follow-up for the pandemic season.
- Subset 1b. The secondary pandemic influenza subset will include subjects:
  - with a follow-up in the CPRD GOLD and in HES during the pandemic season including 01 October 2009 and the preceding 180 days period (from 04 April 2009), AND
  - with a GP questionnaire returned and with all needed information available after review based on quality check of data,
    AND
  - with at least one rejection reported in HES, in the CPRD GOLD or in the GP questionnaire, within the subject's follow-up for the pandemic season.

Seasonal influenza study period (01 September 2006 – 31 August 2009):

- Subset 2a. The primary seasonal influenza subset will include subjects with a follow-up during at least one of the influenza seasons (2006/2007, 2007/2008 or 2008/2009) in the CPRD GOLD and in HES. The subject's follow-up must include:
  - 01 September and the preceding 180 days period (from 05 March) in the CPRD GOLD and in HES,
    AND
  - at least one rejection reported in HES in at least one of the 3 influenza seasons.
- Subset 2b. The secondary seasonal influenza subset will include subjects:
  - with a completed GP questionnaire returned and containing all information needed for the analyses,
    AND
  - with a follow-up during at least one of the influenza seasons (2006/2007, 2007/2008 or 2008/2009) in the CPRD GOLD and in HES. The subject's follow-up must include:
    - 01 September and the preceding 180 days period (from 05 March) in the CPRD GOLD and in HES,
      AND
    - at least one rejection reported in HES, or in the CPRD GOLD or in the GP questionnaire, in at least one of the 3 influenza seasons.

Figure 3. Data source for case selection for subsets a and subsets b



Statistical methods – 3) Covariates

[…]
Time since transplantation: The period following any transplantation will be divided into four periods corresponding to different risk periods: day 0-30, 31-90, 91-180 and >180. The category >180 days will be the reference in the analyses. If the date of transplantation is missing, a missing category will be defined. All data from the CPRD GOLD, HES and from the GP questionnaire will be used, prioritising information from the GP questionnaire.

[…]

If the risk periods of several events of the same covariate are overlapping, a combined risk period will span from the start date of the first event to the end date of the last event.

For all covariates except Time since transplantation and previous rejection, in case of incomplete dates of events reported in the GP questionnaire, two options are considered:

- *If the period defined by the incomplete date includes record(s) of the covariate in the CPRD GOLD and/or HES, the corresponding record(s) will be used to determine the associated risk period.*
- *If no record from CPRD GOLD and/or HES is included in the unknown period, the median of the unknown part (day or month) will be imputed. For instance, --/JUN/2010 changed into 15/JUN/2010, or --/---/2010 changed into 02/JUL/2010.*

[…]

Time since transplantation: The period following any transplantation will be divided into four periods corresponding to different risk periods: day 0-30, 31-90, 91-180 and >180. The category >180 days will be the reference in the analyses. The detailed approach to detect the events is provided in Appendix A. For the primary analyses only data from CPRD GOLD and HES will be considered. For the secondary analyses additional information related to transplantations reported in the GP questionnaires will be also taken into consideration.

[…]

For all covariates except time since transplantation, if the risk periods of several events of the same covariate are overlapping, a combined risk period will span from the start date of the first event to the end date of the last event. For time since transplantation, the risk periods associated with the most recent transplantation will be considered.

Statistical methods – 4) Descriptive Statistics

Frequency tables will be generated for categorical variables. Mean, median, standard deviation, minimum, maximum will be provided for continuous data such as age.

The following characteristics will be presented:
- *Disposition of the study population (Appendix D, Table 2 to Table 5);*
- *Distribution of subjects and person-time in each influenza season, for each population subset (Appendix D, Table 6);*
- *Description of influenza vaccine exposure (0, 1, 2 doses) for each season, and for each population subset (Appendix D, Table 7 and Table 8);*
- *Age and time since transplantation at the beginning of each season, gender, region of GP practice the subject is registered with, number of transplantations during each season, number of rejections within 180 days before the beginning of each season, reasons for end of follow-up (e.g.*

death, new transplantation, end of study period), and infections/chronic conditions during each season (i.e., respiratory infection, acute bacterial infection, chronic viral infection, opportunistic infection, malignancies/cancers) for each population subset and overall (Appendix D, Table 9 and Table 10).

Frequency tables will be generated for categorical variables. Mean, median, standard deviation, minimum, maximum will be provided for continuous data such as age.

The following characteristics will be presented:

- Disposition of the study population (Appendix D, Table 2 to Table 5);
- Distribution of subjects and person-time in each influenza season, for each population subset (Appendix D, Table 6);
- Description of influenza vaccine exposure (0, 1, 2 doses) for each season, and for each population subset (Appendix D, Table 7 and Table 8);
- Age and time since transplantation at the beginning of each season, gender, region of GP practice the subject is registered with, number of transplantations during each season, number of rejections within 180 days before the beginning of each season, reasons for end of follow-up (e.g. death, new transplantation, end of study period), and infections/chronic conditions during each season (i.e., respiratory infection, acute bacterial infection, chronic viral infection, opportunistic infection, malignancies/cancers, chemotherapy) for each population subset and overall. For subsets 1a and 2a the data from the GP questionnaires will not be considered (Appendix D, Table 9 and Table 10).

Statistical methods – 5) Statistical Analyses – Primary objective

The risk period will be 31 days (day 0 to day 30) after each dose of Pandemrix™ and the control period will correspond to the subject's follow-up during the season 2009/2010, excluding the risk period.

The primary analysis will be based on Subset 1a (primary pandemic influenza subset). Only rejection events reported in the GP questionnaire will be taken into account. The approach to identify rejection(s) is detailed in Appendix A. No restriction regarding the type of rejection or the immunological mechanism involved will be applied. Only the first rejection after vaccination will be considered. If several rejections occur during the follow-up, the subject will be censored at the second rejection.

Primary analysis for the primary objective:

- *Number of rejections and person-time in each risk and control period associated with Pandemrix™ vaccination: control before vaccination, risk after dose1, control after dose1, risk after dose2, control after dose2, etc. (Appendix D, Table 11).*
- *RI estimates associated with Pandemrix™ vaccination (all doses pooled) adjusted for time since transplantation (Appendix D, Table 12).*
- *RI estimates associated with Pandemrix™ vaccination adjusted for time since transplantation and seasonal influenza vaccination (Appendix D, Table 13).*
- *RI estimates associated with Pandemrix™ vaccination adjusted for time since transplantation and for each infection/ chronic condition, malignancy/cancer and chemotherapy in separate models (Appendix D, Table 13).*
- *RI estimates associated with Pandemrix™ vaccination adjusted for time since transplantation, for seasonal influenza vaccination and for all infections/ chronic conditions, malignancy/cancer and chemotherapy (Appendix D, Table 13).*

Sensitivity analyses for the primary objective:

- *RI estimates associated with Pandemrix™ vaccination (all doses pooled) adjusted for time since transplantation using the standard SCCS method [Farrington, 1995] (Appendix D, Table 13).*
- *If more than 5% of subjects from Subset 1a have incomplete rejection dates reported in the GP questionnaire (year and month documented but day missing) and no rejection reported in the CPRD GOLD and/or HES during the month indicated in the GP questionnaire, all analyses detailed above will be conducted with the incomplete dates imputed as follows: --/ MM/YYYY changed into 01/ MM/YYYY, 15/ MM/YYYY or 30 (or 31 or 29 or 28 depending on the specific month)/ MM/YYYY.*
- *If more than 5% of rejections reported in the GP questionnaire are chronic or of unknown type, these rejections will not be included in the sensitivity analyses.*

Secondary analyses for the primary objective:
All the above analyses will be repeated for Subset 1b (secondary pandemic influenza subset)

- *with data from the CPRD GOLD/HES only, and*
- *with data from the CPRD GOLD/HES and from the GP questionnaire, prioritising information from the GP questionnaire for rejections. The approach to identify the rejections for each of these sets is described in Appendix A.*

Exploratory analyses for the primary objective:

A previous rejection might influence the risk of a subsequent rejection. Although this effect is partially controlled in the case-series design if it is considered constant during the study period, it could modify the effect of vaccination, or could be time-dependent. Thus, the effect of previous rejection(s) on the risk of subsequent rejection(s) will be investigated through the following sequential analyses:

The modifying effect of a previous rejection will be tested by introducing an interaction term between the fixed effect of a previous rejection and the time-varying effect of vaccination in the model. The fixed effect will be a binary variable: at least one rejection during the 180-day period before 01 October 2009, or no rejection during this period. The interaction will be tested in the model with adjustment for time since transplantation.

Number of cases allowing, a stratified analysis will be conducted:

- *Subjects with no rejection episode before the beginning of the pandemic influenza season, or with rejection episode(s) having occurred >180 days before the beginning of the pandemic influenza season. RI estimate associated with vaccination adjusted for time since transplantation.*
- *Subjects with at least one rejection episode during the 180-day period prior to the pandemic influenza season. RI estimate associated with vaccination adjusted for time since transplantation and adjusted for the risk period associated with previous rejections.*

These exploratory analyses will be based on Subset 1b (secondary pandemic influenza subset). Only subjects with data available during the 180-day period before 01 October 2009 will be considered. Data from the CPRD GOLD/HES and from the GP questionnaire will be used.

Planned analyses will be conducted pooling all organs; additional analyses by organ will be conducted only if 10 rejections are observed for a given organ.

The risk period will be 31 days (day 0 to day 30) after each dose of Pandemrix™ and the control period will correspond to the subject's follow-up during the season 2009/2010, excluding the risk period.

The primary analysis will be based on Subset 1a (primary pandemic influenza subset). Only rejection events reported in the HES will be taken into account. The approach to identify rejection(s) is detailed in Appendix A. Only the first rejection after 1 October 2009 will be considered. If several rejections occur during the follow-up, the subject will be censored at the second rejection.

Primary analysis for the primary objective:

- Number of rejections and person-time in each risk and control period associated with Pandemrix™ vaccination: control before vaccination, risk after dose1, control after dose1, risk after dose2, control after dose2, etc. (Appendix D, Table 11).
- RI estimates associated with Pandemrix™ vaccination (all doses pooled) adjusted for time since transplantation (Appendix D, Table 12).
- RI estimates associated with Pandemrix™ vaccination adjusted for time since transplantation and seasonal influenza vaccination (Appendix D, Table 13).
- RI estimates associated with Pandemrix™ vaccination adjusted for time since transplantation and for each infection/ chronic condition and malignancy/cancer in separate models (Appendix D, Table 13).
- RI estimates associated with Pandemrix™ vaccination adjusted for time since transplantation, for seasonal influenza vaccination and for all infections/ chronic conditions and malignancy/cancer (Appendix D, Table 13).

Sensitivity analyses for the primary objective:

- RI estimates associated with Pandemrix™ vaccination (all doses pooled) adjusted for time since transplantation using the standard SCCS method [Farrington, 1995]. All rejection events (first and subsequent) will be considered (Appendix D, Table 13).

Secondary analyses for the primary objective:

All the above analyses will be repeated for Subset 1b (secondary pandemic influenza subset). Data from the CPRD GOLD/HES and from the GP questionnaires will be considered. In addition to the adjustment for time since transplantation and for each infection/ chronic condition and malignancy/cancer, RI estimates will be adjusted for chemotherapy. The approach to identify the rejections is described in Appendix A. If more than 5% of the rejections are reported in the GP questionnaire to be chronic or of unknown type, a sensitivity analysis excluding these rejections will be performed.

Exploratory analyses for the primary objective:

A previous rejection might influence the risk of a subsequent rejection. Although this effect is partially controlled in the case-series design if it is considered constant during the study period, it could modify the effect of vaccination, or could be time-dependent. Thus, the effect of previous rejection(s) on the risk of subsequent rejection(s) will be investigated through the following sequential analyses:

The modifying effect of a previous rejection will be tested by introducing an interaction term between the fixed effect of a previous rejection and the time-varying effect of vaccination in the model. The fixed effect will be a binary variable: at least one rejection during the 180-day period before 01 October 2009, or no rejection during this period. The interaction will be tested in the model with adjustment for time since transplantation.

Number of cases allowing, a stratified analysis will be conducted:

- Subjects with no rejection episode before the beginning of the pandemic influenza season, or with rejection episode(s) having occurred >180 days before the beginning of the pandemic influenza season. RI estimate associated with vaccination adjusted for time since transplantation.
- Subjects with at least one rejection episode during the 180-day period prior to the pandemic influenza season. RI estimate associated with vaccination adjusted for time since transplantation and adjusted for the risk period associated with previous rejections.

These exploratory analyses will be based on Subset 1a (primary pandemic influenza subset). Data from the CPRD GOLD and HES will be used.

Planned analyses will be conducted pooling all organs. In addition, despite limited statistical power associated with the analyses based on 10 exposed cases, additional analyses by organ will be conducted only if a minimum of 10 rejections are observed for a given organ.

Statistical methods – 5) Statistical Analyses – Tertiary objectives

Assuming that rejection events are not independent across the three seasons, data from influenza seasons 2006/2007, 2007/2008 and 2008/2009 will be analysed separately.

For each season, only subjects with follow-up available will be considered for the analyses. The risk periods will span from day 0 to day 30, or from day 0 to day 60, after each seasonal influenza vaccination; the control period will correspond to any period of the follow-up, excluding the risk period.

The primary analysis will be based on Subset 2a (primary seasonal influenza subset). Only rejection events reported in the GP questionnaire will be taken into account. The approach to identify rejection(s) is detailed in Appendix A. No restriction regarding the type of rejection or the immunological mechanism involved will be applied. Only the first rejection after vaccination will be considered. If several rejections occur during the follow-up, the subject will be censored at the second rejection.

Primary analyses for the tertiary objectives:

- *Number of cases and person-time in the risk period and control periods (Appendix D, Table 14);*
- *RI estimates associated with seasonal influenza vaccination adjusted for time since transplantation (Appendix D, Table 15).*
- *RI estimates associated with seasonal influenza vaccination adjusted for time since transplantation and for each infection/chronic condition, malignancy/cancer and chemotherapy in separate models (Appendix D, Table 15).*
- *RI estimates associated with seasonal influenza vaccination adjusted for time since transplantation and for all infections/ chronic conditions, malignancy/cancer and chemotherapy (Appendix D, Table 15).*

Sensitivity analyses for the tertiary objectives:

- *RI estimates associated with the seasonal influenza vaccination exposure adjusted for time since transplantation using the standard SCCS method [Farrington, 1995] (Appendix D, Table 16).*
- *If more than 5% of subjects from Subset 1a have incomplete rejection dates reported in the GP questionnaire (year and month documented but day missing) and no rejection reported in the CPRD GOLD and/or HES during the month indicated in the GP questionnaire, all analyses detailed above will be conducted with the incomplete dates imputed as follows: --/*

MM/YYYY changed into 01/ MM/YYYY, 15/ MM/YYYY or 30 (or 31 or 29 or 28 depending on the specific month)/ MM/YYYY.

- *If more than 5% of rejections reported in the GP questionnaire are chronic or of unknown type, these rejections will not be included in the sensitivity analyses.*

Secondary analyses for the tertiary objectives:
All the above analyses will be repeated for Subset 2b (secondary seasonal influenza subset)

- *with data from the CPRD GOLD/HES only, and*
- *with data from the CPRD GOLD/HES and from the GP questionnaire, prioritising information from the GP questionnaire for rejections. The approach to identify the rejections for each of these sets is described in Appendix A.*

Exploratory analyses for the tertiary objectives:

The modifying effect of a previous rejection will be tested for each season by introducing an interaction term between the fixed effect of a previous rejection and the time-varying effect of seasonal influenza vaccination in the model. The fixed effect will be a binary variable: at least one rejection during the 180-day period before the beginning of the influenza season, or no rejection during this period. The interaction will be tested in the model with adjustment for time since transplantation.

Number of cases allowing, a stratified analysis will be conducted for each influenza season:

- *Subjects with no rejection episode before the beginning of the influenza season, or with rejection episode(s) having occurred >180 days before the beginning of the influenza season. RI estimate associated with vaccination adjusted for time since transplantation.*
- *Subjects with at least one rejection episode during the 180-day period prior to the influenza season. RI estimate associated with vaccination adjusted for time since transplantation and adjusted for the risk period associated with previous rejections.*

These analyses will be based on Subset 2b (secondary seasonal influenza subset). Only subjects with data available during the 180-day period before 01 September will be considered for each season. Data from the CPRD GOLD/HES and from the GP questionnaire will be used.

Planned analyses will be conducted pooling all organs; additional analyses by organ will be conducted only if 10 rejections are observed for a given organ.

Assuming that rejection events are not independent across the three seasons, data from influenza seasons 2006/2007, 2007/2008 and 2008/2009 will be analysed separately. However additional analyses will be also carried out combining all seasons.

For each season, only subjects with follow-up starting at least 180 days before 01 September will be considered for the analyses. The risk periods will span from day 0 to day 30, or from day 0 to day 60, after each seasonal influenza vaccination; the control period will correspond to any period of the follow-up, excluding the risk period.

The primary analysis will be based on Subset 2a (primary seasonal influenza subset). Only rejection events reported in the HES will be taken into account. The approach to identify rejection(s) is detailed in Appendix A. Only the first rejection after 01 September will be considered. If several rejections occur during the follow-up, the subject will be censored at the second rejection.

For the analyses of pooled seasons, the beginning of the study period for each individual will be the 01 September of the first season with 180 days available in HES before 01 September.

Primary analyses for the tertiary objectives:

- Number of cases and person-time in the risk period and control periods (Appendix D, Table 14);
- RI estimates associated with seasonal influenza vaccination adjusted for time since transplantation (Appendix D, Table 15).
- RI estimates associated with seasonal influenza vaccination adjusted for time since transplantation and for each infection/chronic condition and malignancy/cancer in separate models (Appendix D, Table 15).
- RI estimates associated with seasonal influenza vaccination adjusted for time since transplantation and for all infections/ chronic conditions and malignancy/cancer (Appendix D, Table 15).

Sensitivity analyses for the tertiary objectives:

- RI estimates associated with the seasonal influenza vaccination exposure adjusted for time since transplantation using the standard SCCS method [Farrington, 1995]. All rejection events (first and subsequent) will be considered (Appendix D, Table 16).

Secondary analyses for the tertiary objectives:

All the above analyses for separate seasons will be repeated for Subset 2b (secondary seasonal influenza subset). Data from the CPRD GOLD/HES and from the GP questionnaires will be considered. In addition to the adjustment for time since transplantation and for each infection/ chronic condition and malignancy/cancer, RI estimates will be adjusted for chemotherapy. The approach to identify the rejections is described in Appendix A. If more than 5% of the rejections are reported in the GP questionnaire to be chronic or of unknown type, a sensitivity analysis excluding these rejections will be performed.

Exploratory analyses for the tertiary objectives:

The modifying effect of a previous rejection will be tested for each season, and pooled seasons by introducing an interaction term between the fixed effect of a previous rejection and the time-varying effect of seasonal influenza vaccination in the model. The fixed effect will be a binary variable: at least one rejection during the 180-day period before the beginning of the influenza season, or no rejection during this period. The interaction will be tested in the model with adjustment for time since transplantation.

Number of cases allowing, a stratified analysis will be conducted:

- Subjects with no rejection episode before the beginning of the influenza season, or with rejection episode(s) having occurred >180 days before the beginning of the influenza season. RI estimate associated with vaccination adjusted for time since transplantation.
- Subjects with at least one rejection episode during the 180-day period prior to the influenza season. RI estimate associated with vaccination adjusted for time since transplantation and adjusted for the risk period associated with previous rejections.

These analyses will be based on Subset 2a (primary seasonal influenza subset). Only the first rejection reported in HES will be considered and subjects will be censored at any subsequent rejection.

Planned analyses will be conducted pooling all organs. In addition, despite limited statistical power associated with the analyses based on 10 exposed cases, additional analyses by organ will be conducted only if a minimum of 10 rejections are observed for a given organ.

Section 1.1 General exclusion criteria on data from CPRD GOLD and HES

In addition to the inclusion/exclusion criteria applied at subject level, the following criteria will be applied to the data of each subject.

Exclusion criteria for data from the CPRD GOLD:

- *"Eventdate" (date of medical event in the CPRD GOLD) or "system date" (date of recording in CPRD GOLD) before the "Current Registration Date (CRD)" or after the "Transfer Out Date (TOD)";*
- *"Eventdate" or "system date" before the "Up To Standard date (UTS)" of the GP practice the subject is registered with and after its "Last Collection Date (LCD)".*
- *All data with "system date" equal to "eventdate" in datasets "clinical" or "referral"*

Exclusion criteria for data from HES:

- *Match to the CPRD GOLD: category other than 'Strong match' (see variable 22 below for description);*
- *"epistart" (start date of episode of care) or "evdate" (date of procedure) before the "start date of HES follow-up" (see variable 20 for description) or after the "end date of HES follow-up" (see variable 21 for description).*

In addition to the inclusion/exclusion criteria applied at subject level, the following criteria will be applied to the data of each subject.

Exclusion criteria for data from the CPRD GOLD:

- "Eventdate" (date of medical event in the CPRD GOLD) or "system date" (date of recording in CPRD GOLD) before the "Current Registration Date (CRD)" or after the "Transfer Out Date (TOD)";
- "Eventdate" or "system date" before the "Up To Standard date (UTS)" of the GP practice the subject is registered with and after its "Last Collection Date (LCD)".

Exclusion criteria for data from HES:

- Match to the CPRD GOLD: subjects not eligible for linkage to HES;
- "epistart" (start date of episode of care) or "evdate" (date of procedure) before the "start date of HES follow-up" (see variable 20 for description) or after the "end date of HES follow-up" (see variable 21 for description).

Appendix E: ALGORITHMS AND CODES FOR DATA EXTRACTION

Section 2.1, Appendix A Subject characteristics

Column name	*Field name*	*Description*	*CPRD GOLD file*	*Codelist*	*Comments*
[…]					
19. Patient identifier in HES	***hesid***	*Unique identifier for a patient in the HES*	*Hes_source*	-	-
20. Start date of HES follow-up	***HESstart***	*Start of valid HES data collection for patient:* *max (01/04/1997, patient's current registration date (crd), practice UTS date)*	*Hes_source*	*dd/mm/yyyy*[1]	*Link to the file patient by the variable patid*
21. End date of HES follow-up	***HESend***	*End of valid HES data collection for patient:* *min (31/10/2009, patient's transfer out date, practice last collection date (lcd))*	*Hes_source*	*dd/mm/yyyy*[1]	*Link to the file patient by the variable patid*
22. Matching CPRD-HES	***Match***	*Flag indicating strength of matching:* *0 = No match (never hospitalised or unable to match identifiers)* *1 = Strong match (linked using NHS, DOB, & gender);* *2 = Matched on DOB, gender, and postcode;* *3 = Weak match*	*Hes_source*	-	*Link to the file patient by the variable patid*

Column name	Field name	Description	CPRD GOLD file	Codelist	Comments
[…]					
19. Patient identifier in HES	**Gen_hesid**	Unique identifier for a patient in the HES	Hes_patient	-	-
20. Start date of HES follow-up	*HESstart*	Start of valid HES data collection for patient: max (01/04/1997, patient's current registration date (crd), practice UTS date)	linkage_coverage	dd/mm/yyyy[1]	

Column name	Field name	Description	CPRD GOLD file	Codelist	Comments
21. End date of HES follow-up	*HESend*	End of valid HES data collection for patient: min (31/10/2011, patient's transfer out date, practice last collection date (lcd))	linkage_coverage	dd/mm/yyyy[1]	
22. CPRD-HES eligibility	*HES_e*	Flag (0,1) indicating whether patient is eligible for linkage to HES data	Hes_patient	-	Link to the file patient by the variable patid

Section 2.2.1, Appendix A Primary analyses: episodes reported in the GP questionnaire

Variables	***Information***
25. Rejection episode	*A number will be attributed to each rejection episode reported in the GP questionnaire, except for episodes reported with a missing date or with the year only. The combination of this number with the subject's "patid" will result in a unique identifier for each rejection episode.* *Only reported episodes that occurred between 01 September 2006 and 31 October 2010 will be considered to build the analysis dataset.* *In the primary analyses, only rejection episodes reported in the GP questionnaire will be considered. For episodes reported with incomplete dates (i.e., day missing), the CPRD GOLD and/or HES (if available) will be used to estimate the date of the event. However, episodes with the day missing will be ignored if an episode with a complete date is reported during the same month in the GP questionnaire. Rejection episodes reported in the GP questionnaire with a missing date or with only the year reported will be ignored.*
26. Start date of the rejection episode	*Complete date from the GP questionnaire or date determined from the CPRD GOLD and/or HES for episodes reported with incomplete dates (i.e., day missing).* *In the CPRD GOLD, the dates to consider are in the variable "eventdate". In HES, it is the "start date" (variable "epistart") of the "episodes of care" for diagnoses and the variable "evdate" for the procedures.* *<u>Determination of the day for episodes reported with incomplete dates (day missing):</u>* *Date of the first of all the following records which occurred during the month documented in the GP questionnaire. Only records for the same organ or with no organ specified will be considered:* - *Records with a medcode from the list in Appendix* F *in CPRD GOLD datasets 'clinical' or 'referral'.* - *Records with an ICD10 code from the list in Appendix* H *in the HES dataset 'hes_diagnosis_epi'.* - *Records with an OPCS code from the list in Appendix* J *in the HES dataset 'hes_procedures_epi'.* *If no record is reported within the corresponding month, the date will remain incomplete, and the episode will only be considered in the sensitivity analyses.*
27. Organ rejected	*Organ as reported in the GP questionnaire.*
28. Type of rejection	*Type of rejection as reported in the GP questionnaire. Four categories of rejection are considered: hyperacute, acute, chronic and unknown.*
29. Immunological mechanism	*Immunological mechanism as reported in the GP questionnaire. Three categories of rejection are considered: humoral, cellular and unknown.*

Variables	*Information*
30. Compliance to immuno-suppressive medication 3 months prior to rejection	*Compliance as reported in the GP questionnaire. Five categories of compliance are considered: no immunosuppressive medication, fully compliant, usually compliant, non-compliant and unknown.*

Variables	**Information**
25. Rejection episode	A number will be attributed to each rejection episode. The combination of this number with the subject's "patid" will result in a unique identifier for each rejection episode. Only records from HES with dates between 05 March 2006 and 31 October 2010 will be considered. The dates to consider are the "start date" (variable "epistart") of the "episodes of care" for diagnoses and the variable "evdate" for the procedures. <u>Identification steps for each episode, by organ:</u> • Records will be identified and chronologically ranked as follows: - Records with an ICD10 code from the list in Appendix H in HES dataset 'hes_diagnosis_epi'. - Records with an OPCS code from the list in Appendix J in HES dataset 'hes_procedures_epi'. • If a record relates to heart and lung as a single code (ICD10 = T863) then the record will be duplicated to have two separate records with the same date for both organs. • The records with no organ specified (ICD10 code in [T868, T869]) will be linked to the organ-specific record closest in time using rejection(s) or transplantation codes (see Appendix G, H, I and J for identifiers). If no organ-specific record is mentioned for a given subject, the organ will remain unspecified. • Within each organ-specific list of records, distinct rejection episodes will be separated by periods of at least 30 days free of rejection records. For rejection(s) of the heart, two episodes will be considered as distinct events, even if separated by less than 30 days, if a new transplantation occurs during this time window. See below for transplantations.

Variables	Information
26. Start date of the rejection episode	Event date of the first record of each episode as defined above.
27. Organ rejected	Organ specified in the rejection episode as defined above in the identification process of the episodes. If the organ cannot be determined, it will stay unspecified.

Section 2.2.2 Appendix A Secondary analyses: CPRD GOLD/HES data:

DELETED

Section 2.2.3 Secondary analyses: combination of GP questionnaires and CPRD GOLD-HES data

Variables	***Information***
34. Rejection episode	*A number will be attributed to each rejection episode. The combination of this number with the subject's "patid" will result in a unique identifier for each rejection episode.* *All data from the CPRD GOLD and/or HES and from the GP questionnaire will be used for to identify the rejection episodes, prioritising information from the GP questionnaire. The rejection episodes reported in the GP questionnaire with a missing date or with only the year reported will be ignored.* *For each subject, only records with dates between 01 September 2006 and 31 October 2010 will be considered to build the dataset. To ensure that none of the rejections included in the analysis have an onset before 01 September 2006, records of all subject will be systematically screened 30 days before this date in the CPRD GOLD and/or HES. In the CPRD, the dates to consider are in the variable "eventdate". In HES, it is the "start date" (variable "epistart") of the "episodes of care" for the diagnoses and the variable "evdate" for the procedures.* *<u>Identification steps for each episode, by organ:</u>* *3) Creation of a list of all records for rejection from the CPRD GOLD and/or HES ('database records') for each organ:* *- Records with a medcode from the list in Appendix* F *in CPRD GOLD datasets 'clinical' or 'referral'.* *- Records with an ICD10 code from the list in Appendix* H *in HES dataset 'hes_diagnosis_epi'.* *- Records with an OPCS code from the list in Appendix* J *in HES dataset 'hes_procedures_epi'.* *- If a record relates to heart and lung as a single code (medcode = 27679 or ICD10 = T863) then the record will be duplicated to have two separate records with the same date for both organs.* *- The records with no organ specified (i.e. medcode in [11113, 29831, 50226] or ICD10 code in [T868, T869]) will be linked to the organ-specific record closest in time using rejection(s) or transplantation codes (see Appendix E, F, G, H, I and J for identifiers), or additional records listed in Appendix K. If no organ-specific record is mentioned for a subject, the organ will remain unspecified.* *4) The following rules will be applied to determine whether rejection records - 'database records' and/or episodes reported in the GP questionnaire ('GP episodes') - correspond to distinct episodes:* *e) 'GP episodes' with a complete date will be considered as distinct episodes.* *A 'GP episode' with incomplete date (i.e., day missing) will also be considered to be distinct if the month does not include a 'GP episode' with a complete date, and includes at least one 'database record' identified in step 1). In the sensitivity analyses, a date will be imputed for 'GP episodes' with incomplete dates; these episodes will be considered as 'GP episodes' with complete dates.*

Variables	***Information***
	f) 'database records' with the same calendar month as a 'GP episode' having an incomplete date, will be associated with this 'GP episode'. *For rejections of the heart, if a new heart transplantation occurs during this calendar month, the 'GP episode' cannot be used because it cannot be determined whether the rejection occurred before or after the new transplantation; the 'database records' in this calendar month will be used using rule d).* *g) 'database records' not classified in b) and within an interval [date - 30 days, date + 30 days] around one or more 'GP episodes' with a complete date, will be associated with the closest 'GP episode'.* *For rejections of the heart, if a new heart transplantation occurs in this interval, the date of the new transplantation will define the lower or upper limit of the interval.* *h) 'database records' not classified in b) or c) will be grouped in strings of records if they are spaced by ≤30 days. A string will constitute a distinct episode if its limits are spaced by >30 days from any 'database record' classified in b) or c).* *For rejections of the heart, if a new heart transplantation occurs in between the 'database records' of a string, the string will be split into two distinct episodes. The detection of the transplantations is described below.*
35. Date of the rejection episode	*The date of each distinct rejection episode will be determined as follows:* - *Date of rejection of the 'GP episode' if the date is complete;* - *First 'database record' of the calendar month of the 'GP episode' if the date is incomplete;* - *Date of the first 'database record' for episodes from 'database records' only.*
36. Organ rejected	*Organ specified in the rejection episode as defined above in the identification process of the episodes. If the organ cannot be determined, it will stay unspecified.*

Variables	*Information*
28. Rejection episode	A number will be attributed to each rejection episode. The combination of this number with the subject's "patid" will result in a unique identifier for each rejection episode. All data from the CPRD GOLD and/or HES and from the reviewed GP questionnaires will be used for to identify the rejection episodes. For each subject, only records with dates between 05 March 2006 and 31 October 2010 will be considered to build the dataset. In the CPRD, the dates to consider are in the variable "eventdate". In HES, it is the "start date" (variable "epistart") of the "episodes of care" for the diagnoses and the variable "evdate" for the procedures. <u>Identification steps for each episode, by organ:</u> 1) Creation of a list of all records for rejection from the CPRD GOLD, from HES ('database records') and from GP questionnaires ('GP records') for each organ: - Records with a medcode from the list in Appendix F in CPRD GOLD datasets 'clinical' or 'referral'. - Records with an ICD10 code from the list in Appendix H in HES dataset 'hes_diagnosis_epi'. - Records with an OPCS code from the list in Appendix J in HES dataset 'hes_procedures_epi'. - If a record relates to heart and lung as a single code (medcode = 27679 or ICD10 = T863) then the record will be duplicated to have two separate records with the same date for both organs. - The records with no organ specified (i.e. medcode in [11113, 29831, 50226] or ICD10 code in [T868, T869]) will be linked to the organ-specific record closest in time using rejection(s) or transplantation codes (see Appendix E, F, G, H, I and J for identifiers), or additional records listed in Appendix K. If no organ-specific record is mentioned for a subject, the organ will remain unspecified. - Episodes reported in the GP questionnaire. In case of incomplete date (day or month missing) if there are 'database records' during the calendar month (if month/year of transplantation documented) or the calendar year (if year only documented) the 'GP record' will be ignored. If no 'database record' is included in the unknown period, the median of the unknown part (day or month) will be imputed. For instance, --/JUN/2010 changed into 15/JUN/2010, or --/---/2010 changed into 02/JUL/2010. 2) Records will be grouped in strings of records if they are spaced by ≤30 days. A string will constitute a distinct episode if its limits are spaced by >30 days from any other string. For rejections of the heart, if new heart transplantation occurs in between the records of a string, the string will be split into two distinct episodes. The detection of the transplantations is described below.

Variables	*Information*
29. Date of the rejection episode	- Event date of the first record of each episode as defined above.
30. Organ rejected	Organ specified in the rejection episode as defined above in the identification process of the episodes. If the organ cannot be determined, it will stay unspecified.

Section 2.3 Appendix A Derived data for transplantations

Variables	*Information*
37. Transplantation event	*A number will be attributed to each transplantation. The combination of this number with the subject's "patid" will result in a unique identifier for each transplantation.* *All data from the CPRD GOLD and/or HES and from the GP questionnaire will be used to identify the transplantations, prioritising information from the GP questionnaire.* *Only records with dates between 01 January 2005 and 31 October 2010 will be considered to build the dataset: variable "eventdate" in the CPRD GOLD; variable "epistart" (start date of the episode of care) for diagnoses, and variable "evdate" for procedures in HES.* *<u>Identification steps for each transplantation, by organ:</u>* *1) Creation of a list of all records for new transplantation from the CPRD GOLD and/or HES ('database records') for each organ:* - *Transplantation records with a medcode from the list [22653, 96423, 72092, 66456, 250, 53626, 61073, 4438, 242, 72939, 58529, 69734, 41495, 9384, 64438, 2997, 55151, 11745, 66705, 24361, 98364, 89924, 96133, 70874, 5504, 5911, 54990, 18774, 4405, 32025, 71422, 89445, 100073, 69194, 97157, 99250, 27319, 9026, 31997, 10461, 96578, 93713, 73743, 38011, 10394 (see Appendix* E *for descriptions)] in the CPRD GOLD datasets 'clinical' or 'referral'.* - *Records with an OPCS code for transplantation from Appendix* I *without M08.4 and M17.4 in HES dataset hes_procedures_epi.* - *If a record relates to heart and lung in a single code (medcode in [250, 53626, 61073] or OPCS code in [K01.1, K01.8, K01.9]), then the record will be duplicated to have two separate records with the same*

Variables	*Information*
	date for both organs. - *The records with no organ specified (i.e. medcode in [22653, 96423, 72092, 66456] will be linked to the organ-specific record closest in time, using rejection(s) or transplantation codes (see Appendix* E, F, G, H, I *and* J *for identifiers), or additional records listed in Appendix* K. *Otherwise, the organ will remain unspecified.* *2) The following rules will be applied to determine whether transplantation records -'database records' and/or transplantations reported in the GP questionnaire ('GP transplantations') - correspond to distinct transplantations:* *a) 'GP transplantations' with a complete date will be considered as distinct transplantations.* *b) 'database records' within an interval [date - 14 days, date + 14 days] around one or more 'GP transplantations' with a complete date, will be associated with the closest 'GP transplantation'. If several OPCS codes for new transplantation (Appendix* I *without M08.4 and M17.4) are within the interval, only the code closest to the 'GP transplantation' will be associated with the 'GP transplantation'; the other OPCS codes in the interval will be treated as distinct transplantations (as in c).* *c) Any new OPCS code for new transplantation (Appendix* I *without M08.4 and M17.4) not classified in b) will identify a distinct transplantation.* *d) 'database records' not classified in b) or c) will be grouped in strings of records if they are spaced by ≤14 days. A string will constitute a distinct transplantation if its limits are spaced by >14 days from any 'database record' classified in b) or c).* *3) 'GP transplantations' with an incomplete date (day or month missing) will be considered to be distinct if there is no 'database record' during the calendar month (if month/year of transplantation documented) or the calendar year (if year only documented).*
38. Date of transplantation	*The date of each distinct transplantation will be determined as follows:* - *Date of 'GP transplantation' if the date is complete.* - *For 'GP transplantations' with an incomplete date (as in 3) above), the date will remain incomplete.* - *If the transplantation is identified from 'database records' only, and by a procedure code (as in 1) above), the transplantation date will be the date of the procedure.* - *Date of the first 'database record' for transplantations from 'database records' only, and with no procedure code.*
39. Organ transplanted	*Organ as identified in the transplantation 'database record' and/or 'GP transplantation', as defined above (37). If the organ cannot be determined, it will remain unspecified.*

Variables	Information
31. Transplantation event	A number will be attributed to each transplantation. The combination of this number with the subject's "patid" will result in a unique identifier for each transplantation. For the main analyses (on subsets 1a and 2a) only data from the CPRD GOLD and HES will be used to identify the transplantations. For the secondary analyses (on subsets 1b and 2b), all available data from the CPRD GOLD, HES or the GP questionnaire will be used. Only records with dates between 05 March 2006 and 31 October 2010 will be considered to build the dataset: variable "eventdate" in the CPRD GOLD; variable "epistart" (start date of the episode of care) for diagnoses, and variable "evdate" for procedures in HES. <u>Identification steps for each transplantation, by organ:</u> 1) Creation of a list of all records for new transplantation from the CPRD GOLD and HES ('database records') for each organ: - Transplantation records with a medcode from the list [22653, 96423, 72092, 66456, 250, 53626, 61073, 4438, 242, 72939, 58529, 69734, 41495, 9384, 64438, 2997, 55151, 11745, 66705, 24361, 98364, 89924, 96133, 70874, 5504, 5911, 54990, 18774, 4405, 32025, 71422, 89445, 100073, 69194, 97157, 99250, 27319, 9026, 31997, 10461, 96578, 93713, 73743, 38011, 10394 (see Appendix E for descriptions)] in the CPRD GOLD datasets 'clinical' or 'referral'. - Records with an OPCS code for transplantation from Appendix I without M08.4 and M17.4 in HES dataset hes_procedures_epi. - If a record relates to heart and lung in a single code (medcode in [250, 53626, 61073] or OPCS code in [K01.1, K01.8, K01.9]), then the record will be duplicated to have two separate records with the same date for both organs. - The records with no organ specified (i.e. medcode in [22653, 96423, 72092, 66456] will be linked to the organ-specific record closest in time, using rejection(s) or transplantation codes (see Appendix E, F, G, H, I and J for identifiers), or additional records listed in Appendix K. Otherwise, the organ will remain unspecified. 2) If applicable: transplantations reported in the GP questionnaire ('GP records') will be added to the 'database records'. In case of incomplete date (day or month missing) if there are 'database records' during the calendar month (if month/year of transplantation documented) or the calendar year (if year only documented) the 'GP records' will be ignored. If no 'database record' is included in the unknown period, the median of the unknown part (day or month) will be imputed. For instance, --/JUN/2010 changed into 15/JUN/2010, or --/---/2010 changed into 02/JUL/2010.

Variables	Information
	3) The following rules will be applied to determine whether transplantation records correspond to distinct transplantations: a) Any new OPCS code for new transplantation (Appendix I without M08.4 and M17.4) will identify a distinct transplantation. b) Other transplantation records within an interval [date - 14 days, date + 14 days] around one or more transplantation procedure (OPCS code) will be associated with the closest transplantation procedure. c) Transplantation records not classified in a) or b) will be grouped in strings of records if they are spaced by 14 days or less. A string will constitute a distinct transplantation if its limits are spaced by >14 days from any transplantation records classified in b) or c).
32. Date of transplantation	The date of each distinct transplantation will be determined as follows: - If the transplantation is identified by a procedure code (as in 2)a) above), the transplantation date will be the date of the procedure. - Date of the first record for transplantations with no procedure code (as in 2)c) above). However if the first record of the transplantations is a 'GP record' with incomplete date, the date of the next record of the transplantation will be selected if available.
33. Organ transplanted	Organ as identified above (37). If the organ cannot be determined, it will remain unspecified.

Section 2.4 Appendix A Derived data for infections and chronic conditions

Variables	***Information***
40. Infection/ chronic condition identifier	*Unique identifier for each infection or chronic condition record. The combination of this identifier with the "patid" will uniquely identify each infection/chronic condition.* *Only records from the CPRD GOLD and/or HES with dates between 01 September 2005 and 31 October 2010 will be considered to build the dataset. Patient records will be systematically screened as far back as September 2005 to ensure that no infection/chronic condition having started before the study period is missed (corresponding to the 365-day risk period for chronic conditions).* *All events reported in the GP questionnaire and all records with a medcode from the list in Appendix* M *in the CPRD GOLD datasets 'clinical' or 'referral' will be included and have an identifier attributed.*
41. Code	*Medcode for events extracted from the CPRD GOLD.*
42. Description	*Description of the infection or chronic condition.* *Data from the GP questionnaire:* *One of the following:* - *Influenza virus infection (Laboratory confirmed)* - *Influenza-like illness* - *Cytomegalovirus (CMV)* - *Herpes Simplex Virus (HSV type 1 or 2)* - *Varicella Zoster Virus (VZV)* - *Chemotherapy* *Data from the CPRD:* *Description of the medcode (Appendix* M*).*

Variables	*Information*
43. Infection/ chronic condition type	*Type of infection or chronic condition:* - *Respiratory infections* - *Acute bacterial infections* - *Chronic viral infections* - *Opportunistic infections* - *Malignancies/cancers* - *Chemotherapy* *Data from the GP questionnaire:* • *Respiratory infections: Influenza virus infection (Laboratory confirmed), Influenza-like illness* • *Opportunistic infections: Cytomegalovirus (CMV), Herpes Simplex Virus (HSV type 1 or 2), Varicella Zoster Virus (VZV)* • *Chemotherapy* *Data from the CPRD:* *See Appendix* M *for identifiers of each type.*
44. Date	*Date reported in the GP questionnaire or event date (variable "evtdate") for events extracted from the CPRD GOLD.* *The incomplete dates of events reported in the GP questionnaires will be managed in the analyses as explained in the main body of this protocol.*
45. Duration of chemotherapy	*Duration of chemotherapy as reported in the GP questionnaire.*

Variables	**Information**
34. Infection/ chronic condition identifier	Unique identifier for each infection or chronic condition record. The combination of this identifier with the "patid" will uniquely identify each infection/chronic condition. Only records with dates between 01 September 2005 and 31 October 2010 will be considered to build the dataset. Patient records will be systematically screened as far back as September 2005 to ensure that no infection/chronic condition having started before the study period is missed (corresponding to the 365-day risk period for chronic conditions). All events reported in the GP questionnaire and all records with a medcode from the list in Appendix M in the

Variables	Information
	CPRD GOLD datasets 'clinical' or 'referral' will be included and have an identifier attributed.
35. Code	Medcode for events extracted from the CPRD GOLD.
36. Description	Description of the infection or chronic condition. Data from the GP questionnaire: One of the following: - Influenza virus infection (Laboratory confirmed) - Influenza-like illness - Cytomegalovirus (CMV) - Herpes Simplex Virus (HSV type 1 or 2) - Varicella Zoster Virus (VZV) - Chemotherapy Data from the CPRD: Description of the medcode (Appendix M).
37. Infection/ chronic condition type	Type of infection or chronic condition: - Respiratory infections - Acute bacterial infections - Chronic viral infections - Opportunistic infections - Malignancies/cancers - Chemotherapy Data from the GP questionnaire: • Respiratory infections: Influenza virus infection (Laboratory confirmed), Influenza-like illness • Opportunistic infections: Cytomegalovirus (CMV), Herpes Simplex Virus (HSV type 1 or 2), Varicella Zoster Virus (VZV) • Chemotherapy Data from the CPRD: See Appendix M for identifiers of each type.

Variables	Information
38. Date	Date reported in the GP questionnaire or event date (variable "evtdate") for events extracted from the CPRD GOLD. In case of incomplete dates of events reported in the GP questionnaires, the median of the unknown part (day or month) will be imputed. For instance, --/JUN/2010 changed into 15/JUN/2010, or --/---/2010 changed into 02/JUL/2010.
39. Duration of chemotherapy	Duration of chemotherapy as reported in the GP questionnaire.

Appendix F: EXAMPLES OF TABLES

Table 4 Number of subjects enrolled into the pandemic influenza part of the study

Title	*Total*	*Percent*
Secondary pandemic influenza subset		-
Subjects with no rejection event reported in the GP questionnaire within their individual follow-up in CPRD GOLD		
Primary pandemic influenza subset		

Title	Total	Percent
Primary pandemic influenza subset		-
Secondary pandemic influenza subset		

Table 5 Number of subjects enrolled into the seasonal influenza part of the study

Title	*Total*	*Percent*
Secondary seasonal influenza subset		
Subjects with no rejection event reported in the GP questionnaire within their complete follow-up periods of any of the seasons 2006/2007, 2007/2008 and 2008/2009.		
Primary seasonal influenza subset		

Title	Total	Percent
Primary seasonal influenza subset		
Secondary seasonal influenza subset		

Table 10 Demographic and baseline characteristics of subjects with data for season <2006-2007> (<seasonal influenza subset>)

		Vaccinated N =		*Not Vaccinated N =*		*Total N =*	
Characteristics	*Parameters or Categories*	*Value or n*	*%*	*Value or n*	*%*	*Value or n*	*%*
Age at 01-Sep-<2006> (years)	*Mean*						
	SD						
	Median						
	Minimum						
	Maximum						
Age group at 01-Sep-<2006> (years)	*0-17*						
	18-44						
	45-60						
	> 60						
Gender	*Female*						
	Male						
Died between 01-Sep-<2006> and 31-Aug-<2007>	*No*						
	Yes						
Time since transplantation at 01-Sep-<2006> (days)	*Not yet**						
	0-30						
	31-90						

		Vaccinated N =		*Not Vaccinated N =*		*Total N =*	
Characteristics	*Parameters or Categories*	*Value or n*	*%*	*Value or n*	*%*	*Value or n*	*%*
	91-180						
	>180						
	Missing						
*Organ transplanted before or during the season***	*Heart*						
	Kidney						
	Liver						
	Lung						
	Pancreas						
	Heart+Lung						
	…						
Number of rejections between 05-Mar-<2006> and 01-Sep-<2006>	*None*						
	At least one						
	Missing						
Number of transplantation events between 01-Sep-<2006> and 31-Aug-<2007>	*0*						
	1						
	2						
	…						
Respiratory infection(s) between 01-Aug-<2006> and 31-Aug-<2007>?	*No*						
	Yes						
Acute bacterial infection(s) between 01-Sep-<2006> and 31-Aug-<2007>	*No*						
	Yes						
Opportunistic infection(s) between 01-Sep-<2006> and 31-Aug-<2007>	*No*						
	Yes						
Chronic viral infection(s) between 01 Sep 2006 and 31-Aug-<2006>	*No*						
	Yes						
Malignancy/cancer(s) between 01 Sep-Aug-<2006> and 31-Aug-<2007>	*No*						
	Yes						
Reasons for end of follow-up	*End of pandemic study period (31-Oct-2010)*						
	New transplantation						
	Death						
	End of CPRD GOLD follow-up						

** Transplantations could happen after 01-Sep-<2006>*

*** Each subject is classified in one category. All combinations are possible*

		Vaccinated N =		Not Vaccinated N =		Total N =	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Age at 01-Sep-<2006> (years)	Mean						
	SD						
	Median						
	Minimum						
	Maximum						

		Vaccinated N =		Not Vaccinated N =		Total N =	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Age group at 01-Sep-<2006> (years)	0-17						
	18-44						
	45-60						
	> 60						
Gender	Female						
	Male						
Died between 01-Sep-<2006> and 31-Aug-<2007>	No						
	Yes						
Time since transplantation at 01-Sep-<2006> (days)	Not yet*						
	0-30						
	31-90						
	91-180						
	>180						
	Missing						
Organ transplanted before or during the season**	Heart						
	Kidney						
	Liver						
	Lung						
	Pancreas						
	Heart+Lung						
	…						
Number of rejections between 05-Mar-<2006> and 01-Sep-<2006>	None						
	At least one						
	Missing						
Number of transplantation events between 01-Sep-<2006> and 31-Aug-<2007>	0						
	1						
	2						
	…						
Respiratory infection(s) between 01-Aug-<2006> and 31-Aug-<2007>	No						
	Yes						
Acute bacterial infection(s) between 01-Sep-<2006> and 31-Aug-<2007>	No						
	Yes						
Opportunistic infection(s) between 01-Sep-<2006> and 31-Aug-<2007>	No						
	Yes						
Chronic viral infection(s) between 01 Sep 2006 and 31-Aug-<2006>	No						
	Yes						
Malignancy/cancer(s) between 01 Sep-Aug-<2006> and 31-Aug-<2007>	No						
	Yes						
Reasons for end of follow-up	End of season (31 August)						
	New transplantation						
	Death						
	End of CPRD GOLD follow-up						

* Transplantations could happen after 01-Sep-<2006>

** Each subject is classified in one category. All combinations are possible

GlaxoSmithKline

Protocol Sponsor Signatory Approval

eTrack study number and Abbreviated Title	116602 (Epi-Flu-H1N1-012 VS UK DB)
ISAC protocol number	12_087R
Date of protocol	Final: 07 September 2012
Detailed Title	A phase IV, retrospective, observational, self-controlled case series analysis in the United Kingdom Clinical Practice Research Datalink GP Online Database to estimate the risk of solid organ transplant rejection following vaccination with Pandemrix
Sponsor signatory	Vivek Shinde, Director, Epidemiology Elderly Vaccines
Signature	[redacted]
Date	10/05/2012

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Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	116602 (EPI-FLU H1N1-012 VS UK DB)
ISAC protocol number	12_087RA
Date of protocol	Final: 07 September 2012
Date of protocol amendment	Amendment 1 Final: 15 July 2013
Detailed Title	A phase IV, retrospective, observational, self-controlled case series analysis in the United Kingdom Clinical Practice Research Datalink GP Online Database to estimate the risk of solid organ transplant rejection following vaccination with Pandemrix™.
Sponsor signatory	Vivek Shinde Director, Influenza - Epidemiology Head of Global Epidemiology
Signature	[redacted]
Date	29 July 2013

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List of Independent Ethics Committees /Institutional Review Boards

The study protocol, the protocol amendment, and other information that required pre-approval were reviewed and approved by the Independent Scientific Advisory Committee (ISAC) of the Clinical Practice Research Datalink General Practitioner OnLine Database (CPRD GOLD).

Signatures of principal or coordinating investigator(s) or sponsor?s responsible medical officer

GlaxoSmithKline Biologicals
Vaccine Value and Health Science
Sponsor Signatory Approval Page

Please note that by signing this page, you take responsibility for the content of the Main Study Report, including appendices

STUDY TITLE: Risk of solid organ transplant rejection following vaccination with Pandemrix? in the United Kingdom

Study: 116602 (EPI-FLU H1N1-012 VS UK DB) Development Phase: N/A

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory: [redacted]

Title of Sponsor Signatory: Director, Lead Epidemiologist,
GSK Biologicals

Signature: _____

Date: _____

Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer

GlaxoSmithKline Biologicals
Vaccine Value and Health Science
Sponsor Signatory Approval Page

Please note that by signing this page, you take responsibility for the content of the Main Study Report, including appendices

STUDY TITLE: Risk of solid organ transplant rejection following vaccination with Pandemrix™ in the United Kingdom

Study: 116602 (EPI-FLU H1N1-012 VS UK DB) Development Phase: N/A

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory: [redacted]

Title of Sponsor Signatory: Director, Lead Epidemiologist, GSK Biologicals

Director Head of Global Epidemiology

Signature: [redacted]

Date: 16 December 2013

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9b6ff23628836d1ac24f5b769ae024a43eaca07d 1.0 12/16/2013 1:24:39 PM - -
495db61501c1cb68f2169e29505da023a450c3a5 1.0 12/16/2013 3:37:52 PM - -
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All references will be available on request.