Risk of solid organ transplant rejection following vaccination with seasonal trivalent inactivated influenza vaccines in England: A self-controlled case-series

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Abstract

Background: Annual seasonal influenza vaccination is recommended for transplant recipients. No formal pharmacoepidemiology study has been published on the association between solid organ transplant (SOT) rejection and vaccination with seasonal trivalent inactivated influenza vaccines (TIIVs).

Methods: The risk of SOT (liver, kidney, lung, heart or pancreas) rejection after TIIV vaccination was assessed using a self-controlled case-series method (NCT01715792). SOT recipients in England with transplant rejection were selected from the Clinical Practice Research DataLink and linked Hospital Episode Statistics inpatient data. The study period (September 2006 to August 2009) encompassed three consecutive influenza seasons. We calculated the relative incidence (RI) of SOT rejection between the 30- and 60-day post-vaccination risk periods and the control periods (any follow-up period excluding risk periods), using a Poisson regression model.

Results: In seasons 2006/07, 2007/08, 2008/09 and pooled seasons, 132, 136, 168 and 375 subjects, respectively, experienced at least one transplant rejection; approximately half (45%–51%) of these subjects had received a TIIV. For season 2006/07, the RI of rejection of any organ, adjusted for time since transplantation, was 0.74 (95% CI: 0.24–2.28) and 0.58 (95% CI: 0.24–1.38) during the 30-day and 60-day risk periods, respectively. Corresponding RIs for season 2007/08 were 1.21 (95% CI: 0.55–2.64) and 1.31 (95% CI: 0.69–2.48); for season 2008/09, 1.09 (95% CI: 0.43–2.28) and 0.64 (95% CI: 0.31–1.33); and for pooled seasons 1.01 (95% CI: 0.58–1.76) and 0.88 (95% CI: 0.56–1.38). The results of a separate analysis of kidney rejections and analyses that took into account additional potential confounders were consistent with those of the main analyses, with 95% CIs including 1 and upper limits below 3.

Conclusion: This study provides reassuring evidence of the safety profile of TIIVs in SOT recipients, thus supporting current recommendations to vaccinate this risk group annually.

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1. Introduction

Compared to the general population, individuals with a compromised immune system are at increased risk of medical complications following influenza virus infection [1]. Solid organ transplant (SOT) recipients are a notable high-risk immune-suppressed population [2]. Influenza virus infection can cause substantial morbidity and mortality in SOT recipients and can trigger acute rejection and chronic allograft dysfunction [3–7]. Consequently, annual seasonal influenza vaccination is recommended for transplant recipients and their close contacts as an important preventative health measure [8].

Although influenza vaccination is generally well tolerated in SOT recipients [9], there is a paucity of robust and conclusive...
evidence regarding the risk of acute cellular and humoral rejection episodes or allograft dysfunction following influenza vaccination [1,2,4]; Several spontaneous case reports in the published literature have suggested a possible association between SOT rejection or early signs of rejection among transplant recipients who had received influenza vaccination during the 2009 H1N1 pandemic influenza [10–12]; One case of pancreas rejection was reported and a small case-control study identified six cases of short-term cellular rejection among heart transplant recipients shortly following receipt of pandemic influenza vaccination during the 2009 H1N1 pandemic [10,11]. De novo anti-HLA antibodies were found in kidney transplant recipients who had received both seasonal and pandemic influenza immunization [12].

In view of these spontaneous case reports and following sporadic post-marketing surveillance reports of SOT rejection after receipt of GSK’s monovalent AS03 (Adjuvant System containing α-tocopherol and squalene in an o/w emulsion) adjuvanted 2009 H1N1 pandemic vaccine (Pandemrix™, GSK Vaccines, Wavre, Belgium), a post-authorisation safety study (PASS) was requested by the European Medicines Agency to assess the risk of SOT rejection following vaccination with Pandemrix™ in the 2009/2010 pandemic influenza season. These results have been reported elsewhere [13]. An additional objective of this study, which is the subject of the present manuscript, was to assess the risk of SOT rejection after immunization with seasonal trivalent inactivated influenza vaccines (TIIVs). Although annually-updated TIIVs have been routinely administered to SOT recipients for several years, no formal pharmacoepidemiology study of their use had been conducted in this patient group. In this study, the risk of organ rejection after vaccination with TIIVs was assessed among SOT recipients who experienced a transplant rejection in England during three consecutive influenza seasons.

2. Methods

In this retrospective, observational database study (ClinicalTrials.gov, NCT01715792), we assessed the risk of SOT (liver, kidney, lung, heart or pancreas) rejection within 30 and 60 days following the receipt of TIIVs using the self-controlled case-series (SCCS) method. This statistical case-only method compares the incidence rate of an event during predefined risk and control periods within a given individual, thereby controlling for individual level confounding factors that do not vary over time [14]. The study period spanned from 1 September 2006 to 31 August 2009, encompassing three consecutive influenza seasons (2006/07, 2007/08 and 2008/09).

The Clinical Practice Research Datalink (CPRD), an observational and interventional research service that operates as part of the UK Department of Health, contains over 4 million active patient records (over 11 million overall) drawn from approximately 675 primary care practices in the UK [15,16]. The population of active patients represents 7% of the total UK population, and CPRD patients have been shown to be representative of the UK general population in terms of age, sex and ethnicity [16]. The CPRD has been granted Multiple Research Ethics Committee approval (05/MRE04/87) to undertake purely observational studies, with external data linkages including Hospital Episode Statistics (HES) and Office for National Statistics mortality data. The work of CPRD is also covered by the National Information Governance Board for Health and Social Care’s Ethics and Confidentiality Committee approval ECC 5-05 (a) 2012. This study was endorsed by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research.

2.1. Subjects and data collection

Cases were identified from patients registered in general practices contributing to the CPRD and with a linked HES inpatient component [17–19] using pre-defined algorithms. The CPRD contains coded longitudinal medical records from general practices in the UK [17] and the HES inpatient database contains details of all admissions to National Health Service (NHS) hospitals in England [19,20]. HES inpatient data linkage is limited to CPRD research-acceptable patients with a valid NHS number, living in England and who belong to a general practice that has agreed to take part in data linkage.

Subjects were eligible for this study if they received a liver, kidney, lung, heart or pancreas transplant and experienced at least one episode of transplant rejection during the study period. Subjects were defined as acceptable for research by the CPRD if they had no follow-up interruptions and information on year of birth, first registration date and gender, and if the data were considered to be of good quality, according to data quality assessments performed by the CPRD team [16]. The study dataset was built using the 2012 third quarter CPRD release, which compiled information from 10,547,532 subjects, with a mean follow-up of 6.8 years, from 644 general practices.

Records of transplantation and transplantation rejection events were identified using pre-defined algorithms based on READ codes in the CPRD and ICD-10 clinical and OPCS-4 procedural codes in the HES linked component (Supplementary Table 1). Multiple transplant rejection episodes for a single individual were considered as new only if they occurred at least 30 days after the previous record of transplant rejection, apart from heart rejections for which all episodes were considered as distinct events. A transplantation episode in an individual was considered as new if reported by OPCS-4 procedural codes or if it occurred more than 14 days since the previous transplant episode.

CPRD code lists for influenza vaccination were developed by querying the CPRD database for relevant product and influenza immunization terms and by using British National Formulary therapy group 14040900 (Supplementary Table 2). The influenza virus strains included in the licensed TIIVs were based on the annual World Health Organization (WHO) recommendations for the Northern Hemisphere [21]. Information on the TIIV brands administered was available for only 10%, 20% and 12% in each of the seasons 2006/07, 2007/08 and 2008/09, respectively.

In order to obtain additional quantitative and qualitative information on identified cases, a standard questionnaire (Supplementary Text 1) was sent to general practitioners (GPs) via the CPRD Research Group in October 2012.

2.2. Statistical analyses

Sample size was estimated for the primary objective of the study (i.e., to assess the risk of SOT rejection following vaccination with Pandemrix™ in the 2009/2010 pandemic influenza season) using relevant information and defined assumptions based on feasibility data (Supplementary Text 2). We found that, with 30 cases, there was 80% power to detect a relative incidence (RI) of 3 or higher. The association between SOT rejection and seasonal vaccination with TIIVs was assessed by calculating the RI of SOT rejection between the 30-day and 60-day post-vaccination risk periods and the control periods, with associated 95% confidence intervals (CIs). The 30-day risk period was defined a priori, based on the observed latency period of spontaneous rejection events reported to GSK’s Global Clinical Safety and Pharmacovigilance among subjects who had received Pandemrix™ and the most common risk period following other exposures such as infection [3]. The case series model is derived from a Poisson cohort model by conditioning on the total
number of events and on the exposures that are experienced by each individual in the cohort over a predetermined observation period [22].

Risk periods covered the 30-day or 60-day period after vaccination with TIVs; the control period corresponded to any period of the study follow-up, excluding risk periods. Since rejection was likely to influence the probability of subsequent vaccination, a modified SCCS method was used, which was developed for situations where occurrence of the event could curtail post-event exposures [14]. The modified SCCS method required subjects to have only one SOT rejection; consequently, only the first SOT rejection was included for each subject and subjects were censored for further rejections. Because censoring at subsequent rejections may not be optimal and to verify the robustness of our results, we performed a sensitivity analysis using the standard SCCS method [23,24] in which subjects were not censored at subsequent rejections.

Separate analyses were conducted for each influenza season. A pooled analysis of the three seasons was also conducted and statistical methods are described in Supplementary Text 3. Subjects with a complete follow-up, starting at least 180 days before 1 September of at least one season, were included in the analyses. The 180-day period was required to accumulate sufficient historical data for subjects. This was to determine if risk periods starting before the analysis period overlapped it, for instance, risk period 91–180 days after transplantation, when transplantation happened within 180 days before the analysis period. Based on a feasibility assessment in the CPRD, we found that the risk of transplant rejection was high within the first month following the transplantation, then declined substantially up to three months and reached its lowest level around six months, with a stable incidence from six months onwards. Because time since transplantation was considered an independent risk factor for SOT rejection, the analyses were adjusted for time since transplantation (risk periods 0–30, 31–90, 91–180 and >180 days) and included additional TIV-unexposed subjects to better account for the effect of this covariate [24]. Supplementary Fig. 1 illustrates the circumstances in which cases were regarded as informative or non-informative for the main analyses. Additional covariates, i.e., bacterial infections, chronic viral infections and cancer/malignancies (risk periods 0–30, 0–365 and 0–365 days, respectively), considered to be independent risk factors for SOT rejection [25], were added to the model provided that information was available for at least five subjects. Since covariate data could also originate from TIV-unexposed subjects, when covariates were added, subjects could potentially be added to the model. Sensitivity analyses were performed focusing on organ-specific data and history of rejection. The effect of previous rejection within 180 days before 1 September of each season on the risk of subsequent rejection could not be investigated because of insufficient sample size (fewer than five subjects). A separate analysis was performed including only subjects without previous rejection within 180 days before the start of the season.

Analyses and data extraction were performed using SAS software version 9.2.

3. Results

3.1. Study population and TIV exposure

A total of 132, 136 and 168 subjects had at least one transplant rejection in seasons 2006/07, 2007/08 and 2008/09, respectively, of whom approximately half (45.4%, 49.3% and 50.6%, respectively) had received a TIV. The distribution of SOT rejections and exposure to TIV during each season is shown in Fig. 1.

Fig. 1. SOT rejections and TIV exposure in each 15-day period between 1 September 2006 and 31 August 2007 (A), 1 September 2007 and 31 August 2008 (B), and 1 September 2008 and 31 August 2009 (C) in subjects with at least one SOT rejection. SOT, solid organ transplantation; TIV, trivalent inactivated influenza vaccine.

The demographic characteristics of subjects were similar across seasons (Table 1). Most subjects (90.2%, 89.7% and 90.5% in 2006/07, 2007/08 and 2008/09, respectively) were followed from 1 September to 31 August. The remaining subjects either died or
were no longer followed in the CPRD because they had left the general practice or the practice was no longer active in the CPRD. Most subjects had records of transplantation or rejection for a single organ (130 in 2006/07, 128 in 2007/08 and 163 in 2008/09). The most common organ transplant rejection was kidney rejection (Table 1).

The characteristics and number of subjects included in the pooled seasonal analyses are presented in Table 2. A total of 375 subjects were considered eligible of whom 175 were exposed to a TIIV. Most subjects received their transplant more than 6 months before the study start. A majority of cases experienced kidney rejections (>60%) and few subjects presented with cancers/malignancies (6.7%).

GP questionnaires were returned for only 140 of 587 (23.9%) subjects with a record of transplant rejection in the CPRD during the period of interest. 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 the CPRD. Information reported on other covariates of interest or compliance to treatment was also very limited. Consequently, the HES inpatient database was used as the sole data source for transplant rejection episodes.

3.2. Risk of SOT rejection following vaccination with a TIIV

3.2.1. Model adjusted for time since transplantation

The study population for the 2006/07 season consisted of 132 subjects who had experienced at least one SOT rejection between 1 September 2006 and 31 August 2007. In that season, one subject had received two TIIV doses and was excluded, leaving 131 subjects for the analysis (Fig. 2). 58 subjects were excluded because they were not informative for the analysis (subjects did not receive TIIV during the analysis period from 1 September to 31 August or they received TIIV only before transplantation during the analysis period). Thus the analyses adjusted for time since transplantation included 74 cases, of whom 55 had received a TIIV; 19 additional unexposed cases were included to better account for the effect of time since transplantation. For season 2007/08, 81 subjects contributed to the analyses; 58 cases had received a TIIV and 23 were unexposed cases. For season 2008/09, 92 subjects contributed to the analyses, of whom 72 were TIIV-exposed and 20 were unexposed cases. Pooling the three consecutive seasons, 375 subjects experienced at least one transplant rejection, of whom 218 were included in the analyses adjusted for time since transplantation and of whom 156 received a TIIV (Figs. 3 and 4).
Table 2
Demographic characteristics of subjects included in the study population for pooled seasonal influenza analysis. All had at least one SOT rejection reported in the Health Episodes Statistics database and follow-up included 1 September. Each subject contributed to only one season, the first with an exposure to TIIV or with an effect of time since transplantation.

<table>
<thead>
<tr>
<th>Age at beginning of analyzed season*, years</th>
<th>Unexposed to TIIV (N = 200)</th>
<th>Exposed to TIIV (N = 175)</th>
<th>Total (N = 375)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (standard deviation)</td>
<td>43.7 (17.8)</td>
<td>53.1 (18.2)</td>
<td>48.1 (18.5)</td>
</tr>
<tr>
<td>Range</td>
<td>1–82</td>
<td>6–90</td>
<td>1–90</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>74 (37.0)</td>
<td>70 (40.0)</td>
<td>144 (38.4)</td>
</tr>
<tr>
<td>Time since transplantation at beginning of analyzed season, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–30 days</td>
<td>2 (1.0)</td>
<td>0</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>31–90 days</td>
<td>5 (2.5)</td>
<td>6 (3.4)</td>
<td>11 (2.9)</td>
</tr>
<tr>
<td>91–180 days</td>
<td>1 (0.5)</td>
<td>6 (3.4)</td>
<td>7 (1.9)</td>
</tr>
<tr>
<td>&gt;180 days or before transplantation</td>
<td>192 (96.0)</td>
<td>163 (93.1)</td>
<td>355 (94.7)</td>
</tr>
<tr>
<td>Organ transplant rejection during season, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>89 (44.5)</td>
<td>109 (62.3)</td>
<td>198 (52.8)</td>
</tr>
<tr>
<td>Liver</td>
<td>19 (9.5)</td>
<td>12 (6.9)</td>
<td>31 (8.3)</td>
</tr>
<tr>
<td>Lung</td>
<td>4 (2.0)</td>
<td>5 (2.9)</td>
<td>9 (2.4)</td>
</tr>
<tr>
<td>Heart</td>
<td>9 (4.5)</td>
<td>10 (5.7)</td>
<td>19 (5.1)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0 (0)</td>
<td>1 (0.6)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Kidney and liver</td>
<td>0 (0)</td>
<td>1 (0.6)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Heart and lung</td>
<td>0 (0)</td>
<td>1 (0.6)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Unspecified§</td>
<td>79 (39.5)</td>
<td>36 (20.6)</td>
<td>115 (30.7)</td>
</tr>
<tr>
<td>Number of organ transplantations received during season, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5 (2.5)</td>
<td>11 (6.3)</td>
<td>16 (4.3)</td>
</tr>
<tr>
<td>1</td>
<td>158 (79.0)</td>
<td>135 (77.1)</td>
<td>293 (78.1)</td>
</tr>
<tr>
<td>2</td>
<td>36 (18.0)</td>
<td>33 (18.9)</td>
<td>69 (18.4)</td>
</tr>
<tr>
<td>Subjects reporting cancer/malignancies, n (%)</td>
<td>12 (6.0)</td>
<td>13 (7.4)</td>
<td>25 (6.7)</td>
</tr>
<tr>
<td>Reasons for end of follow-up other than end of season, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died</td>
<td>10 (5.0)</td>
<td>15 (8.6)</td>
<td>25 (6.7)</td>
</tr>
<tr>
<td>End of CPRD follow-up</td>
<td>7 (3.5)</td>
<td>3 (1.7)</td>
<td>10 (2.7)</td>
</tr>
</tbody>
</table>

CPRD, Clinical Practice Research Datalink; SOT, solid organ transplant; TIIV, trivalent inactivated influenza vaccine.

* Season started 1 September 2006, 2007 or 2008.
§ The code for transplant rejection was a general code without any organ specified.
§ 180-day period before start of season.

Fig. 2. Subjects included in self-controlled case-series (SCCS) analyses of each influenza season. Some subjects contributed to several seasons. Some subjects were exposed to a trivalent inactivated influenza vaccine during the season but were not considered as such in the SCCS analyses because transplantation was after vaccination or they were censored at a second rejection before vaccination. * To be eligible, subjects had to have a follow-up that included 1 September. § One subject received two doses of TIIV in season 2006/07 and was excluded. HES, Hospital Episode Statistic; SOT, solid organ transplantation.

For season 2006/07, the RI of rejection of any organ, adjusted for time since transplantation, was 0.74 (95% CI: 0.24–2.28) and 0.58 (95% CI: 0.24–1.38) during the 30-day and 60-day risk periods after vaccination, respectively (Fig. 4). Corresponding RIs for the 2007/08 season were 1.21 (95% CI: 0.55–2.64) and 1.31 (95% CI: 0.69–2.48) and for the 2008/09 season, 0.99 (95% CI: 0.43–2.28) and 0.64 (95% CI: 0.31–1.33) (Fig. 4). In the pooled seasons analyses, results were consistent with the separate season analyses, with RIs of 1.01 (95% CI: 0.58–1.76) and 0.88 (95% CI: 0.56–1.38) during the 30-day and 60-day risk periods after vaccination, respectively (Fig. 4).

Similar results were observed in a sensitivity analysis using the standard SCCS method: for each season, 95% CIs included 1 and upper limits remained below 3 within the 30-day and 60-day risk periods (Fig. 4). Results from the sensitivity analyses of data pooled
from all three seasons were consistent with those from the individual season analyses, with 95% CI upper limits below 2 (Fig. 4).

3.2.2. Analyses further adjusted for cancer/malignancies

In multivariable analyses that included other covariates in addition to time since transplantation, RI could be computed for cancer/malignancies only, due to the low number of exposed subjects (fewer than five) for other covariates (bacterial infections and chronic viral infections). For seasons 2006/07, 2007/08, 2008/09 and pooled seasons, 75, 81, 93 and 210 cases, respectively, contributed to the analyses. The number of subjects who had received a TIIV was 54 in season 2006/07, 55 in 2007/08, 72 in 2008/09 and 152 in the pooled seasons. The RI of transplant rejection of any organ during the 30-day and 60-day risk periods after vaccination, adjusted for time since transplantation and cancer/malignancies was 0.79 (95% CI: 0.25–2.49) and 0.63 (95% CI: 0.26–1.51), respectively, for season 2006/07, 1.29 (95% CI: 0.59–2.85) and 1.43 (95% CI: 0.75–2.72) for season 2007/08 and, 0.99 (95% CI: 0.43–2.28) and 0.64 (95% CI: 0.31–1.32) for season 2008/09 (Fig. 4). For pooled seasons, the RIs during the 30-day and 60-day risk periods after vaccination were 1.06 (95% CI: 0.61–1.84) and 0.92 (95% CI: 0.59–1.45) respectively.

3.2.3. Analyses restricted to kidney transplant rejection

When transplant rejections were classified by organ, the number of cases was sufficient for a separate analysis of kidney transplanted patients only. For seasons 2006/07, 2007/08, 2008/09 and pooled seasons, 49, 57, 63 and 144 kidney rejection cases were considered, respectively, of whom 36, 40, 47 and 98 had received a TIIV. The RI of kidney rejection during the 30-day risk period was 0.59 (95% CI: 0.13–2.63), 1.28 (95% CI: 0.52–3.15), 0.98 (95% CI: 0.34–2.80) and 0.91 (0.44–1.87) in seasons 2006/07, 2007/08, 2008/09 and pooled seasons, respectively (Fig. 4). Corresponding RIs during the 60-day risk period were 0.50 (95% CI: 0.16–1.60), 0.82 (95% CI: 0.36–1.86), 0.42 (95% CI: 0.15–1.21) and 0.59 (95% CI: 0.32–1.08), respectively.

3.2.4. Analyses restricted to patients with no previous transplant rejections

A separate analysis was performed for the group of subjects who did not experience any rejections within 6 months before the start of the season (i.e. 1 September). In seasons 2006/07, 2007/08, 2008/09 and pooled seasons, 65, 75, 78 and 204 cases were considered, respectively, of which 47, 52, 58 and 143 had received a TIIV. The RI of SOT rejection during the 30-day risk period was 0.66 (95% CI: 0.19–2.33), 1.10 (95% CI: 0.47–2.55), 1.01 (95% CI: 0.41–2.49) and 1.04 (95% CI: 0.59–1.84) in seasons 2006/07, 2007/08, 2008/09 and pooled seasons, respectively. RIs during the 60-day risk period remained within the same range and all 95% CIs included 1, with upper limits below 3 for individual seasons and below 2 for the pooled seasons (Fig. 4).

4. Discussion

Although transplant recipients remain a high priority group for annual seasonal influenza vaccination in many national influenza vaccination programmes, little is known about the safety profile with regards to risk of transplant rejection following TIIV administration. In addition, epidemiological data produced during the 2009 influenza pandemic have confirmed that SOT patients remain at high risk of influenza-associated complications, namely viral and bacterial pneumonia, hospitalization and even death [26,27].

Recent papers assessed the association between monovalent pandemic influenza vaccination and the occurrence of transplant rejection focusing on the 2009/2010 pandemic influenza season [13,28], but none has investigated such an association focusing on TIIVs. It was therefore important to formally assess the risk of SOT rejection associated with seasonal TIIVs in a pharmacoepidemiology study.

We therefore assessed the risk of transplant rejection among SOT recipients following vaccination with seasonal TIIVs in England throughout three consecutive influenza seasons using a self-controlled case-series method. In the analyses adjusted for time since transplantation, over 200 subjects experienced at least one transplant rejection in any of the seasons, of whom approximately 70% had received TIIVs. There was no evidence of an increased risk of SOT rejection within 30 or 60 days after TIIV vaccination, with 95% CIs of RI estimates including 1 and upper limits not exceeding 3 for separate influenza seasons and below 2 where seasons were pooled. Analyses that took into account potential confounders (malignancies or lack of rejection episodes within 180 days before each season) were consistent with these results. The most common transplanted organ was the kidney; a separate analysis restricted to kidney recipients showed no increased risk of kidney rejection following vaccination with TIIVs.

A strength of this study was the use of CPRD and linked HES inpatient data. The CPRD has been extensively used in pharmacoepidemiology research, with data internally and externally validated for various outcomes [29]. Use of HES inpatient information maximized the likelihood of capturing SOT rejections, an outcome most likely clinically managed in hospital settings. In the initial identification of transplanted patients in the CPRD, a high proportion (93%; data not shown) had a HES linkage available, which confirmed the appropriateness of this approach. In addition, since the HES uses a standardized coding system (ICD-10 clinical and OPcs-4 procedural coding), consistent information was ensured across the study population [19]. Also, to account for heterogeneity across influenza seasons arising from the
dominant circulating virus strains [30], the virulence of specific strains, as well as WHO recommendations on TIIV strain composition [21], three consecutive seasons were considered separately and in pooled analyses. This allowed us to assess the risk, taking into account potential variability from one influenza season to another, and to evaluate the overall risk using a more comprehensive approach. Indeed, in Europe, while vaccine strains were well matched to circulating strains in 2006/2007, the two subsequent seasons (2007/2008 and 2008/2009) were characterized by a sub-optimal match between vaccine strains and circulating strains, especially for type B viruses [30]. This is of particular importance to this study given the fact that natural infection caused by influenza is considered a major independent risk factor for transplant rejection [9].

Another strength of the study included the use of the SCCS method, which is case-based and inherently adjusts for fixed
confounders such as gender, genetic predisposition, health and socio-economic status, healthcare-seeking behaviour and access to healthcare, while controlling for indication bias. In the present study, as vaccination with TIVs could not be assumed to be fully independent of transplant rejection, a modified SCCS method was used [14], in which only the first SOT rejection was included for each subject. In sensitivity analyses, risk estimates were also calculated using the standard SCCS method [23], in which subjects were not censored at subsequent rejections. The results were consistent with those calculated using the modified SCCS method.

A potential limitation of this study was the lack of complementary information on clinical events or conditions that may influence SOT rejection, such as viral/bacterial infection, underlying medical conditions, non-compliance with immunosuppressive treatment, diabetes and timing of antiviral therapy [1,2,9]. To overcome this limitation, for all eligible subjects experiencing a transplant rejection in the study period, standardized questionnaires were sent to GPs in order to gather complementary medical history information. However, these were returned for less than a quarter of subjects with a record of transplant rejection in the CPRD during the period of interest, of whom fewer than half were identified by GPs and reported in the questionnaires as having a SOT rejection, and there was a lack of useful complementary information. Since this suggested that SOT rejection was under-reported and under-documented in primary care records, the HES inpatient database was used as the sole data source to capture transplant rejection episodes.

Determining the risk period was another challenge, given that little is known about the potential mechanism and duration of effect of influenza vaccination on the immune response that could theoretically be associated with SOT rejection. Two risk periods were considered to evaluate the association between seasonal influenza vaccination and SOT rejection. A 30-day risk period was used based on the latency period of reported spontaneous rejection events among subjects who received Pandemrix™ and the most common risk period following other exposures such as infection [3]. Using a longer risk period (60-day), estimates remained within the same range as those for the 30-day risk period. Further study limitations included the lack of case adjudication to verify the medical history of transplanted patients or the inability to fully assess the recent effect of time since transplantation since most subjects had received their organ at least 180 days before the influenza season start. In addition, the effect of previous rejections and risk estimates for organ rejections other than the kidney could not be computed because of low numbers of subjects who experienced rejections within six months before the start of any season.

Furthermore, there was not enough detail recorded in the CPRD to perform an analysis by TIV brand. However, seasonal vaccines are manufactured using similar processes and all contain the same strains as per WHO annual recommendations. Although influenza viruses included in cell-based vaccines are grown in cultured cells of mammalian origin rather than hens’ eggs, cell-based vaccines are similar to egg-based influenza vaccines. Therefore, we can reasonably conclude that the results reflect the overall “average” safety profile of TIVs used during the three influenza seasons.

In conclusion, we found no evidence of an increased risk of SOT rejection following vaccination with TIVs in three consecutive influenza seasons using the SCCS method. Although additional research is needed to determine formally if the finding in renal transplant recipients can be extended to other SOT subgroups as well as to all TIV brands, our study presents reassuring evidence of the safety profile of TIVs when administered to SOT recipients. The results provide quantitative safety information for healthcare professionals, policy makers and recommendation bodies and support current recommendations to vaccinate this high-risk population yearly in order to prevent influenza and related complications.

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Trademarks: Pandemrix is a trademark of the GSK group of companies.

Conflict of interest statement: This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. However, the interpretation and conclusions contained in this report are under the sole responsibility of the authors.

GDS’s company received consulting fees from the GSK group of companies for the work submitted for publication and for other projects. FH, CC, DW, JL and DR are employees of the GSK group of companies. CC, DW, JL and DR have stocks, stock options or restricted shares ownership in the GSK group of companies. GLCF and VS were employed by the GSK group of companies when the study was conducted.

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Authors’ contribution to the manuscript: GDS, FH, CC, DR, and VS participated in the conception and design of the study. GDS, FH, CC, DW, JL, DR, and VS assessed the feasibility of the study in CPRD/HES. FH assembled the dataset and analyzed the data with support from DR and GLCF. DW and JL provided CPRD/HES expertise. All authors contributed to the interpretation of the results. GDS and FH wrote the manuscript. All authors had full access to the data (including statistical reports and tables), reviewed the manuscript, gave final approval before submission, and can take responsibility for the accuracy of the data analysis and the integrity of the results. GDS and FH contributed equally to the manuscript. GDS (the manuscript’s guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2016.05.016.

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