Vaccine 33 (2015) 5458–5463

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Influenza vaccination and risk of stroke: Self-controlled case-series study

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ARTICLE INFO

Article history:
Received 11 November 2014
Received in revised form 24 April 2015
Accepted 5 August 2015
Available online 18 August 2015

Keywords:
Influenza vaccination
Influenza
Stroke
Transient ischaemic attack
Self-controlled case-series method

ABSTRACT

Background: Stroke may be triggered by respiratory infections, including influenza. Influenza vaccination could therefore reduce risk of stroke. Previous studies of this association have shown conflicting results. We aimed to investigate whether influenza vaccination was associated with reduced risk of stroke.
Methods: We used a self-controlled case series design. The General Practice Research Database (GPRD) was used to extract records of patients aged 18 years or over recorded with stroke (fatal or non-fatal) from September 2001 to May 2009. Statistical modelling with conditional Poisson regression was employed to compute incidence rate ratios (IRR). The incidence rate of stroke in fixed time periods after influenza vaccination was compared with the incidence rate during a baseline period.
Results: There were 17,853 eligible individuals who received one or more influenza vaccinations and experienced a stroke during the observation period. The incidence of stroke was significantly reduced in the first 59 days following influenza vaccination compared with the baseline period. We found reductions of 55% (IRR 0.45; 95% CI 0.36–0.57) in the first 1–3 days after vaccination, 36% (0.64; 0.53–0.76) at 4–7 days, 30% (0.70; 0.61–0.79) at 8–14 days, 24% (0.76; 0.70–0.84) at 15–28 days and 17% (0.83; 0.77–0.89) at 29–59 days after vaccination. Early vaccination between 1 September and 15 November showed a greater reduction in IRR compared to later vaccination given after mid-November.
Conclusions: Influenza vaccination is associated with a reduction in incidence of stroke. This study supports previous studies which have shown a beneficial association of influenza vaccination for stroke prevention.

1. Introduction

Stroke is an important cause of mortality and morbidity, with health service costs even excluding social and economic costs in the UK estimated at around £2.8 billion per year [1]. Non-modifiable risk factors for stroke such as age and family history, and modifiable factors including hypertension [1] are present in only 50 to 60% of patients with ischaemic strokes, suggesting that there may be other triggers [2].

A systematic review of the potential triggers of ischaemic stroke found 12 studies citing infection including respiratory infection as a potential trigger, with a significant association between ischaemic stroke and infection within the previous week (OR = 2.91; 95% CI, 1.41 to 6.00) or month (OR = 2.41; 95% CI, 1.78 to 3.27) [3]. Influenza has been particularly implicated [4,5], where a tripling of the influenza rate was associated with about a 6% change in stroke occurrence rate [5].

This raises the possibility that treatment or prevention of influenza might also prevent stroke. Antibiotics have been shown to be ineffective in preventing stroke [6], and there are doubts about the effectiveness of antivirals for influenza [7]. There is a possibility that influenza vaccination may be preventative for strokes.

Influenza vaccination has been associated with a reduced risk of stroke in several observational studies [8–12], either alone or combined with pneumococcal vaccine [13]. Other studies have not confirmed this [14–16], and concern remains that bias and residual confounding may explain these conflicting findings [17]. Key sources of bias include the healthy vaccinee effect, where those at

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http://dx.doi.org/10.1016/j.vaccine.2015.08.013
0264-410X/

lower risk from stroke are more likely to be vaccinated [18], and in contrast the effect of functional status [19], where people who are frailer are less likely to be vaccinated and more likely to suffer stroke.

We previously carried out a nested case-control study to examine the association between influenza vaccination and stroke risk, and found a 24% reduction in the risk of stroke associated with influenza vaccination given within the same influenza season [20]. Although we adjusted for comorbidity and attempted to account for functional ability and frailty using general practice consultation and home visit rates, the results are still susceptible to residual confounding, particularly from the 'healthy vaccinee' effect, Due to this and the inconclusive evidence from other studies we aimed to further investigate the association between influenza vaccination and stroke using a self-controlled case series (SCCS) design, since this design implicitly accounts for all fixed confounders.

2. Methods

2.1. Study design

We used a self-controlled case series (SCCS) design to investigate the association between stroke and influenza vaccination. The SCCS method compares incidence of stroke in cases only during different time periods following vaccination, with incidence during a baseline period. In this method, cases act as their own controls in the baseline period when they are not exposed to vaccination. By using cases only the SCCS method has the advantage of implicitly adjusting for all measured and unmeasured fixed confounding variables, and so can help to identify true causal effects [21,22]. The SCCS method therefore implicitly adjusts for unknown confounders such as functional ability which are not routinely recorded in clinical records or databases provided that they do not vary with time during the observation period. We have used this method in a previous study investigating the association between influenza vaccination and acute myocardial infarction (AMI) [23].

Data for the study were extracted from the General Practice Research Database (GPRD), now called the Clinical Practice Research Datalink (CPRD), a large computerised anonymised database representative of and comprising around 5% of the population of England and Wales [24]. The GPRD includes demographic information, health behaviours, referrals and treatment outcomes, with good clinical information including stroke and deaths [25]. Data are entered into clinical records by general practitioners (GPs) at the time of consultation, and recorded using Oxford Medical Information Systems (OXMIS) and Read codes. The study received independent UK National Health Service ethics approval.

2.2. Study population and data sources

The study cases were drawn from all quality assured (up-to-standard) practices included in the GPRD over a period of eight years. Cases included patients aged 18 years or over recorded with stroke (fatal or non-fatal) registered with the GPRD practices from 1/09/2001 to 31/08/2009. Cases with a diagnosis of stroke prior to the start of the observation period were excluded from the study.

We limited cases to those that had been registered with the same GP for five years preceding the date of diagnosis of stroke to ensure completeness of recording. Inclusion was also restricted to cases who had received an influenza vaccination at least once during the observation period and to those cases where stroke occurred after the first vaccination to ensure that all patients were eligible for influenza vaccination during the observation period [26]. Cases not meeting these criteria were excluded.

The incident or index date of stroke diagnosis was defined as the first date when the GP recorded a medical diagnosis code (as defined above) for fatal/non-fatal stroke on the patient's clinical or referral record. Cases were excluded if the stroke incident date was identical to any of their influenza vaccination dates within the observation period because of the possibility that vaccination was given after the stroke occurred or that the stroke was recorded retrospectively on the influenza vaccination date (Fig. 1).

2.3. Sample size calculation

Based on a two-sided 5% significance level and 90% power in order to detect an IRR of 0.9, a sample size of 6520 cases was required, assuming that 65% of the population were vaccinated and that 50% of the observation period would be an exposure risk period [27].

2.4. Statistical analyses

Statistical modelling was done using conditional Poisson regression in Stata (version 12) to compute the incidence rate ratios (IRR). The incidence rates of stroke in the risk periods after influenza vaccination were compared with the incidence rates during the baseline period. Influenza is typically seasonal and to take account of this in the analysis calendar time was used as the underlying time line. The start of the observation period was taken from the date of the first influenza vaccination recorded after 1/09/2001. The end of the observation period was either 31/05/2009 or the date of leaving the practice or death which ever occurred first. The baseline period was taken as the interval between 6 months (180 days) after vaccination or the following 30th April which ever occurred first up to 14 days before the next vaccination.

Seasonality was included in the models by dividing the risk periods into one of four quarterly seasons: September to November; December to February; March to May and June to August. Age was grouped into $\leq$64 years and $\geq$65 years at baseline. We tested for interactions of influenza vaccination with age at the start of the observation period. Seasonally adjusted IRRs split by gender and vaccination timing were calculated. The vaccination timings were split into early (1 September to 15 November) and late (16 November to 30 April) vaccinations.

2.5. Cut-off points for exposure and baseline

Cut-off points for risk periods and seasons were calculated and intervals between any two adjacent cut-off points determined for each year within the observation period. There were eight predefined risk periods including: the baseline period; 1–14 days before vaccination and; 1–3 days; 4–7 days, 8–14 days; 15–28 days; 29–59 days; 60–90 days; 91–120 days; 121–180 days post vaccination. The reason 1–14 days pre-vaccination was considered as a separate interval was due to the fact that a stroke occurring during this period is likely to affect the subsequent likelihood of receiving an influenza vaccination. A reduced and statistically significant IRR during this period could indicate that vaccinations were less likely to be given in the first two weeks after a stroke.

3. Results

We identified 21,981 first cases of stroke within the observation period; 4128 cases that either had not received any influenza vaccinations within the observation period or had a stroke diagnosis before their first vaccination date or on the same date as one of their vaccinations were excluded. For the final analysis therefore 17,853 cases of stroke were included comprising 52.8% (9424) females and 47.2% (8429) males. The median age at first stroke diagnosis was