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

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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.

Keywords: influenza vaccination, influenza, stroke, transient ischaemic attack, self-controlled case-series method

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 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.

Methods

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.

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 (Figure 1).

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]

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 ≤64 years and ≥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.

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 pre-defined 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.

Results

We identified 21981 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 17853 cases of stroke were included comprising 52.8% (9424) females and 47.2% (8429) males. The median age at first stroke diagnosis was 75 years (interquartile range 68-81 years) and 85.7% (15303) were aged 65 and over.

There was a significant reduction in the rate of stroke between 15 and 59 days following vaccination. Significant reductions in risk were also apparent in the 1-14 days before and 1-14 days after vaccination (Table 1), possible reasons for which are discussed below. 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, 0.77-089) at 29-59 days after vaccination.

The incidence rate ratios for influenza vaccination were similar in men and women
There were reduced risks with early vaccination up to 59 days after vaccination, but no significant reductions for late vaccinations although numbers were small and so confidence intervals were wide (Table 2).

There was no significant interaction between age at the start of the observation period and the effect of influenza vaccination ($p = 0.07$, data not shown). We found no significant difference between patterns of risk in males and females ($p = 0.25$).

Discussion

Influenza vaccination was associated with a significant reduction in incidence of stroke in the first 59 days following vaccination. This protective effect of influenza vaccination, presumably due to prevention of stroke triggered by influenza, waned over four months following vaccination and was not statistically significant after 59 days.

An apparent reduction in risk 1-14 days before vaccination may have been due to patients being less likely to receive an influenza vaccination in the 14 days after stroke or possibly due to late entry of vaccination data. The reduction in risk in the 1-3 days post-vaccination may be due to individuals being more likely to receive vaccination when they are feeling well, whereas individuals with prodromal symptoms of stroke or at immediate high risk of stroke may have been less likely to attend the GP for influenza vaccination because they were either hospitalised or too unwell for vaccine administration. The same may be true for the period 4-7 days after vaccination but the vaccine could be conferring immunity by this time also.[28] The reduction in stroke incidence at 8-59 days is more likely to be due to a true effect of influenza vaccine reducing the risk of influenza-induced stroke.

Strengths and limitations

We used a large, representative and robust research database with sufficient power to detect effects with precision. We minimized selection bias by including all cases of stroke within the selected time period.[29] We recognise that restricting our sample to patients who had been at the same general practice for five years could exclude certain groups, for example transient populations, those with a less settled lifestyle or older people who had moved into a care home, but it did ensure completeness of vaccination information.

The SCCS design is more robust than other observational designs in comparing differences in outcomes within an individual over time, thus adjusting for unknown or unmeasured confounders that do not change over time while measuring differences that occur between people. It is therefore better at accounting for 'healthy vaccinee' effects and functional status, unlike other observational designs.[22] Since the SCCS method only accounts for known and unknown confounders do not change over time, a caveat of the study design is that it does not account for within-person confounding due to confounders varying over the observational period. If an individual's cardiovascular risk factors increase over the observation period then the likelihood of receiving the vaccine will also increase.[23] To counter this effect we restricted our observational period in the analysis to include only time after the first recorded vaccination: any time prior to the first vaccination was excluded from the observation period.

Within-person study designs may have lower precision and greater susceptibility to bias when long-term exposures are analysed particularly from changing exposure

probability.[30] Our study design contained a period of fairly constant influenza risk and we assumed the influenza vaccination was protective over the entire influenza season albeit with waning efficacy.

Comparison with existing literature

A beneficial effect of influenza vaccination for preventing stroke[8-11] has been found in previous observational studies[20] in contrast with studies showing no effect of vaccination[14, 15] or suggesting that the association is due to bias.[17] Our findings are also in line with previous studies showing an association between influenza vaccination and reduction in risk of AMI, particularly for early influenza vaccination,[23, 31] but no reduction in risk with pneumococcal vaccination.[31]

An early effect of vaccination is plausible because 59% of influenza vaccine recipients have protective antibody titres within one week of vaccination. The antibody response against influenza lasts four to six months.[32]

A previous self-controlled case series study of risk of vascular events following respiratory infection or influenza vaccination, conducted by Smeeth and colleagues using a similar study design and data source,[10] showed a risk reduction associated with a period up to 28 days following vaccination. Compared with this study, they used shorter risk periods and included an exposure period which extended up to 91 days after vaccination with the remaining observation time included in the baseline period. Our study showed significant benefits up to 59 days following vaccination. This difference may reflect the choice of the baseline period where an assumption of constant risk needs to be postulated and the differences in post-vaccination risk periods selected. We assumed that the vaccine could offer protection over the entire influenza season.[28, 32] The baseline period in our study therefore included a period of fairly constant influenza risk compared with Smeeth et al who used a baseline period with more variable influenza risk.[23]

The mechanism by which influenza might precipitate stroke is not known but has been postulated to be due to various factors including non-specific immune stimulation,[33] fever leading to endothelial dysfunction, hypercoagulability or increased viscosity, and stress or metabolic changes in response to infection. Influenza may cause atheroma,[34] affect carotid plaque stability or promote rupture.[35]

Implications for future research

Our findings support current recommendations for influenza vaccination in people at high risk,[36] but with the added effect of stroke prevention. If shown to be a causal effect, this may help improve suboptimal vaccination rates, particularly in at-risk groups.[37] Early influenza vaccination was associated with greater reduction in stroke risk compared with later vaccination which should encourage early vaccination.

The uncertainty about whether to extend vaccination to younger adults at risk of stroke, suggests that experimental studies are needed to confirm these findings, and before recommending changes in indications or timing of vaccination.

If a causative link between influenza vaccination and reduction in stroke risk is confirmed by experimental studies and leads to higher vaccinations rates there would be significant benefits for patient and population health.

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Conflict of interest disclosures
All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. None of the authors had any conflict of interest.

Ethics
We sought and received approval for the study from the Independent Scientific Advisory Committee (ISAC) of the GPRD, National Research Ethics Service (NRES) and NHS Lincolnshire Research Management and Governance (previously Lincolnshire Teaching Primary Care Trust) [05/MRE04/87]. The study also received ethical approval from the University of Lincoln, School of Health and Social Sciences Ethics Committee.

Author contributions
Zahid Asghar had full access to all of the data in the study and takes responsibility for the integrity and accuracy of the data analysis.
Study concept and design: Siriwardena, Coupland, Asghar
Acquisition of data: Siriwardena
Analysis and interpretation of data: Siriwardena, Coupland, Asghar.
Drafting of the manuscript: Asghar, Siriwardena
Critical revision of the manuscript for important intellectual content: Coupland, Asghar, Siriwardena.
Statistical analysis: Asghar, Coupland.
Obtained funding: Siriwardena, Coupland.
Administrative, technical, or material support: None.
Study supervision: Siriwardena, Coupland.

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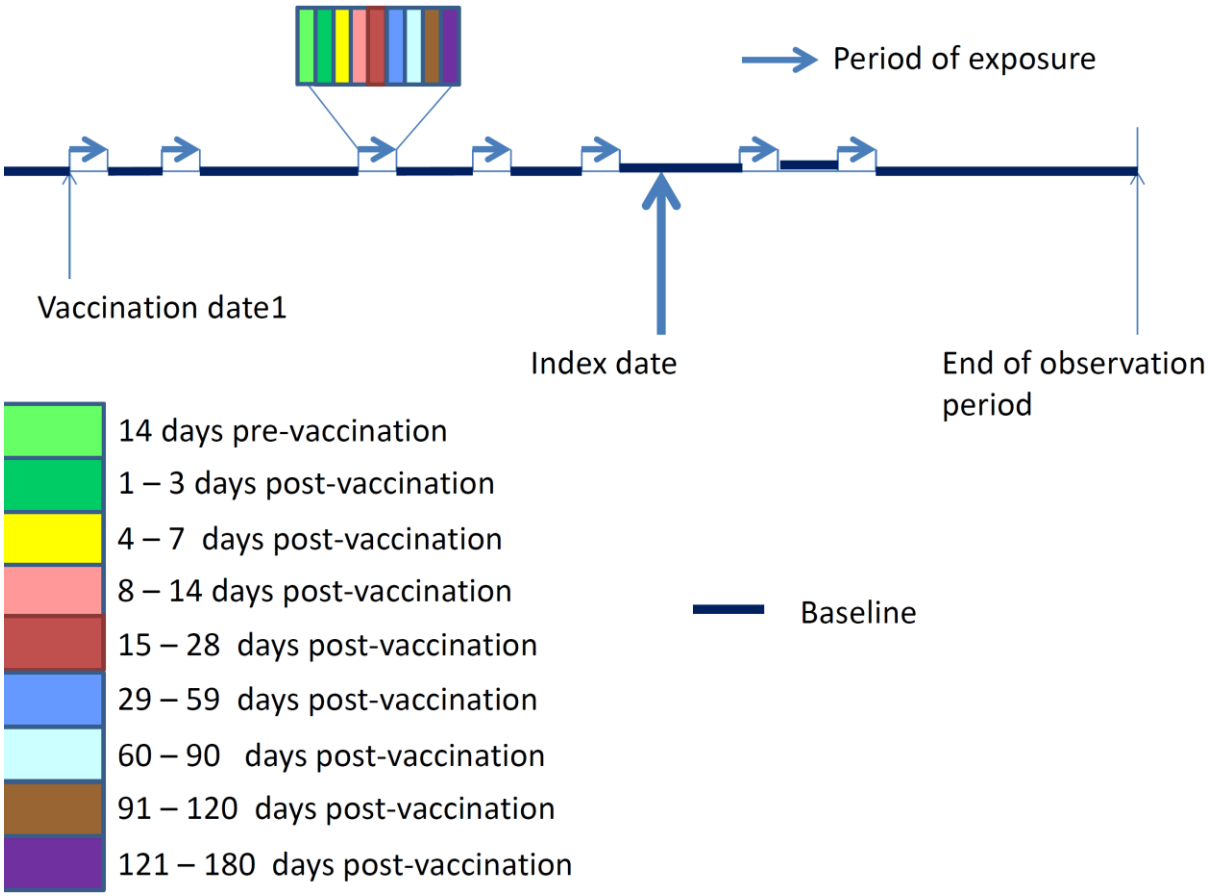
Figure 1 Study design: exposure and baseline period



Observation period starts at vaccination date1

Table 1 Association between influenza vaccination and stroke

Risk period	Number of cases		Time at risk (person years)	Adjusted[a]	
	N	%		IRR[b]	95% CI
Baseline period[c]	10001	56.0	53738	1·00	-
Pre vaccination interval					
1-14 days	334	1.9	2983	0.55	0.49 - 0.61
Post vaccination intervals					
1-3 days	72	0.4	733	0.45	0.36 - 0.57
4-7 days	134	0.8	978	0.64	0.53 - 0.76
8-14 days	256	1.4	1710	0.70	0.61 - 0.79
15-28 days	552	3.1	3417	0.76	0.70 - 0.84
29-59 days	1268	7.1	7545	0.83	0.77 - 0.89
60-90 days	1388	7.8	7506	0.95	0.88 - 1.03
91-120 days	1363	7.6	7212	0.99	0.92 - 1.06
121-180 days	2485	13.9	13266	1.02	0.97 - 1.08

[a] Adjusted for seasonality
[b] IRR incidence rate ratio.
[c] Baseline period is between 180 days or 30th of April (whichever came first) after vaccination and 14 days prior to next vaccination

Table 2 Seasonally adjusted IRR by gender and vaccination timing for stroke

Risk period (days)	Gender						Vaccination timing					
	Female			Male			Early (1 September to 15 November)			Late (16 November to 30 April)		
	Cases	Adjusted		Cases	Adjusted		Cases	Adjusted		Cases	Adjusted	
	N	IRR[a]	95% CI	N	IRR	95% CI	N	IRR	95% CI	N	IRR	95% CI
Baseline period	5349	1	-	4652	1	-	10097	1	-	17757	1	-
Pre vaccination interval												
1-14 days	170	0.54	0.46 - 0.64	164	0.65	0.47 - 0.65	330	0.55	0.49 - 0.61	4	0.49	0.18 - 1.31
Post vaccination intervals												
1-3 days	35	0.42	0.30 - 0.59	37	0.48	0.35 - 0.67	70	0.45	0.35 - 0.57	2	0.78	0.19 - 3.15
4-7 days	56	0.51	0.39 - 0.66	78	0.78	0.62 - 0.98	132	0.64	0.53 - 0.76	2	0.59	0.15 - 2.37
8-14 days	138	0.72	0.60 - 0.86	118	0.68	0.56 - 0.82	251	**0.70**	**0.61 - 0.79**	5	0.84	0.35 - 2.04
15-28 days	298	0.79	0.70 - 0.89	254	0.74	0.64 - 0.84	538	**0.76**	**0.69 - 0.83**	14	1.18	0.69 - 2.03
29-59 days	639	0.78	0.71 - 0.86	629	0.88	0.80 - 0.97	1240	**0.83**	**0.77 - 0.88**	28	1.13	0.77 - 1.66
60-90 days	757	0.95	0.86 - 1.05	631	0.96	0.86 - 1.07	1363	0.96	0.89 - 1.03	25	1.10	0.73 - 1.64
91-120 days	693	0.93	0.84 - 1.03	670	1.07	0.96 - 1.18	1351	1.00	0.93 - 1.08	12	0.68	0.38 - 1.21
121-180 days	1289	1.01	0.94 - 1.09	1196	1.04	0.97 - 1.13	2481	1.03	0.97 - 1.08	4	0.83	0.31 - 2.21

[a] Adjusted for seasonality

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