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

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Summary of talk

• Background and motivation
• Previous studies
• Study aim and method
• Analysis and Results
• Conclusions
Background

- Stroke is a major cause of death and long term illness
- 5% of UK population are affected, around 130 thousand suffer a new or recurrent stroke each year
- Common risk factors such as age, gender, smoking, diabetes .., don’t account for all the stroke cases
- Emerging evidence shows that respiratory infections and incidence of strokes may be related
Previous studies

- Contradictory evidence: Small study size
- Design Bias: recall, therapeutic
- Confounding: ‘healthy user effect’, missing different treatments and differences in health behaviours in vaccinees.
Study aim

To investigate whether influenza vaccination was associated with a reduced risk of stroke.
Method

- Vaccination season from 01 Sept 2001-31 Aug 2009
Method

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Vaccination periods:

- 14 days pre-vaccination
- 14 days post-vaccination
- 15 -28 days post-vaccination
- 29 - 59 days post-vaccination
- 60 -90 days post-vaccination
- 91-120 days post-vaccination
- 121-180 days post-vaccination
Method

- Exposure-Base line **cut points**

Prestart → Vaccination date → Index date → End of observation period → Period of exposure
Method

• **Case**: medical diagnostic Read/OXMIS codes for first stroke entered by GP

• **Index date**: first date when GP recorded stroke code (fatal/non-fatal) in clinical/referral record

• In the case-series method the Cases act as Controls
Method

- Cut-off points for risk periods and seasons were calculated for each year.

- There were eight pre-defined risk periods including: the baseline period for each interval: 1-14 days before vaccination and; 1-14 days; 15-28 days; 29-59 days; 60-90 days; 91-120 days; 121-180 days post vaccination.
Method

• 1-14 days pre-vaccination considered as a separate interval: a stroke event occurring during this period is likely to affect the subsequent likelihood of receiving an influenza vaccination.

• Seasonality was included by dividing the risk periods into one of four quarterly seasons: Sept. to Nov.; Dec. to Feb.; March to May and June to Aug.
Method

• The vaccination timings were split into:

  Early (1 September to 15 November) and

  Late (16 November to 30 April) vaccinations.
Analysis

- The incidence rate of stroke in fixed time periods after vaccination was compared with the incidence rate during a baseline period.

- Statistical modelling with conditional Poisson regression in Stata 12 was employed to compute incidence rate ratios (IRR).
Descriptive statistics

- 21,981 first cases of stroke within the observation period

- 4,128 cases that either did not receive influenza vaccination or had a stroke diagnosis on or before the vaccination date were excluded
Descriptive statistics

- 17,853 cases of stroke considered for the final analysis.
- 52.8% (9,424) females and 47.2% (8,429) males.
- The median age at first stroke diagnosis was 75 years (interquartile range 68-81 years).
- 85.7% were aged 65 and over.
Main results

Association between influenza vaccination and stroke

<table>
<thead>
<tr>
<th>Risk period</th>
<th>Number of cases</th>
<th>Time at risk (person years)</th>
<th>IRR</th>
<th>Adjusted 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>base line period</strong></td>
<td>N</td>
<td>%</td>
<td>IRR</td>
<td>Adjusted 95% CI</td>
</tr>
<tr>
<td>Pre Vac 1-14 days</td>
<td>334</td>
<td>3.0</td>
<td>0.55</td>
<td>0.49 - 0.61</td>
</tr>
<tr>
<td>Post Vac 1-14 days</td>
<td>462</td>
<td>3.5</td>
<td>0.63</td>
<td>0.57 - 0.69</td>
</tr>
<tr>
<td>15-28 days</td>
<td>552</td>
<td>3.4</td>
<td>0.76</td>
<td>0.70 - 0.84</td>
</tr>
<tr>
<td>29-59 days</td>
<td>1268</td>
<td>7.6</td>
<td>0.83</td>
<td>0.77 - 0.89</td>
</tr>
<tr>
<td>60-90 days</td>
<td>1388</td>
<td>7.6</td>
<td>0.95</td>
<td>0.88 - 1.03</td>
</tr>
<tr>
<td>91-120 days</td>
<td>1363</td>
<td>7.3</td>
<td>0.99</td>
<td>0.92 - 1.06</td>
</tr>
<tr>
<td>121-180 days</td>
<td>2485</td>
<td>13.4</td>
<td>1.02</td>
<td>0.97 - 1.08</td>
</tr>
</tbody>
</table>

*a* Adjusted for seasonality  
*b* IRR incidence rate ratios.  
*c* Baseline is between 180 days or 30th of April (whichever came first) after vaccination and 14 days prior to next vaccination.
## Main results

**Seasonally adjusted IRR by gender and timing of vaccination**

<p>| Risk period (days) | Gender | Vaccination timing |<br />
|--------------------|--------|---------------------|---|
|                    | Female | Early (1 September to 15 November) | Late (16 November to 30 April) |</p>
<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>IRR**</th>
<th>Adjusted IRR</th>
<th>Adjusted IRR</th>
<th>IRR</th>
<th>Adjusted IRR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base line period</strong></td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td><strong>Pre-vaccination 1-14 days</strong></td>
<td>0.54</td>
<td><strong>0.55</strong></td>
<td>0.46 - 0.64</td>
<td><strong>0.55 - 0.68</strong></td>
<td>0.45</td>
<td>0.17 - 1.21</td>
</tr>
<tr>
<td><strong>Post-vaccination 1-14 days</strong></td>
<td>0.6</td>
<td><strong>0.62</strong></td>
<td>0.52 - 0.69</td>
<td><strong>0.57 - 0.69</strong></td>
<td>0.74</td>
<td>0.38 –1.45</td>
</tr>
<tr>
<td>15-28 days</td>
<td>0.79</td>
<td><strong>0.75</strong></td>
<td>0.70 - 0.89</td>
<td><strong>0.69 - 0.83</strong></td>
<td>1.16</td>
<td>0.68 – 2.00</td>
</tr>
<tr>
<td>29-59 days</td>
<td>0.78</td>
<td><strong>0.83</strong></td>
<td>0.71 - 0.86</td>
<td><strong>0.77 - 0.88</strong></td>
<td>1.11</td>
<td>0.76 –1.63</td>
</tr>
<tr>
<td>60-90 days</td>
<td>0.95</td>
<td><strong>0.96</strong></td>
<td>0.86 - 1.05</td>
<td><strong>0.89 - 1.03</strong></td>
<td>1.08</td>
<td>0.72 –1.61</td>
</tr>
<tr>
<td>91-120 days</td>
<td>0.93</td>
<td><strong>1.00</strong></td>
<td>0.84 - 1.03</td>
<td><strong>0.93 - 1.08</strong></td>
<td>0.67</td>
<td>0.38 –1.19</td>
</tr>
<tr>
<td>121-180 days</td>
<td>1.01</td>
<td><strong>1.03</strong></td>
<td>0.94 - 1.09</td>
<td><strong>0.97 - 1.08</strong></td>
<td>0.82</td>
<td>0.30 –2.18</td>
</tr>
</tbody>
</table>

All IRRs are adjusted for seasonality.
Study strengths and limitations

• We used a large, representative and robust research database with sufficient power to detect effects with precision.

• Selection bias was minimized by including all cases of stroke within the selected time period.

• Confounders are taken into account naturally assuming that they don’t change over the observational period.
Study strengths and limitations

• Since the method assumes that the confounders do not change over the observational period: it does not account for **within-person** confounding due to confounders varying over the observational period.

• We counter this effect by restricting the observational period at first vaccination date.
Conclusion

- Influenza vaccination in the preceding season is associated with a reduction in incidence of stroke. This study supports previous studies which have shown a beneficial association of influenza vaccination in stroke prevention.
Acknowledgments

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• Participants/CPRD

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Thank you