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Key Points:

- we investigated population-level associations between the timing of myocardial infarction or stroke hospital admissions and laboratory-confirmed respiratory infections
- infection with HMPV, RSV, influenza, rhinovirus and adenovirus was associated with increased ischaemic stroke and MI risk in the elderly

Running title: Respiratory infection & vascular events

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Abstract:

Background

Acute respiratory infections are associated with increased risk of myocardial infarction (MI) and stroke, however, the role of different organisms is poorly characterised.

Methods

We undertook a time-series analysis of English hospital admissions for MI and stroke (age-stratified: 45-64, 65-74, 75+ years), laboratory-confirmed viral respiratory infections and environmental data for 2004-2015. Weekly counts of admissions were modelled using multivariable Poisson regression with weekly counts of respiratory viruses (influenza, parainfluenza, rhinovirus, respiratory syncytial virus (RSV), adenovirus or human meta-pneumovirus (HMPV)) investigated as predictors. We controlled for seasonality, long-term trends and environmental factors.

Results

Weekly hospital admissions in adults aged 45+ years averaged 1347 (IQR 1217-1541) for MI and 1175 (IQR 1023-1395) for stroke. Median numbers of respiratory infections ranged from 11 cases per week (IQR 5-53) for influenza to 55 (IQR 7-127) for rhinovirus. In the adjusted models, all viruses except parainfluenza were significantly associated with MI and ischaemic stroke admissions in those aged 75+. Among 65-74 year olds, adenovirus, rhinovirus and RSV were associated with MI but not ischaemic stroke admissions. Respiratory infections were not associated with MI or ischaemic stroke in people aged 45-64, nor with haemorrhagic stroke in any age group. An estimated 0.4-5.7% of MI and ischaemic stroke admissions may be attributable to respiratory infection, with greater excess burden during weeks with high circulating virus levels.
Conclusions

We identified small but strongly significant associations in the timing of respiratory infection (with HMPV, RSV, influenza, rhinovirus and adenovirus) and MI or ischaemic stroke hospitalisations in the elderly.

**Keywords:** myocardial infarction, stroke, respiratory infection, epidemiology
Background

Globally, ischaemic heart disease is the leading cause of death[1]. Over the past two decades population growth and ageing have facilitated a rising burden of ischaemic heart disease despite falling levels of age-standardised incidence and case-fatality of acute myocardial infarction (MI) in most world regions[1, 2]. Previous studies have shown a transient risk of acute vascular events including MI and cardiovascular deaths after clinically diagnosed acute respiratory infections (ARIs) from GP or hospital records[3-5]. Influenza vaccine reduces the risk of major adverse cardiac events among people with existing cardiovascular disease[6]. However few ARIs are laboratory-confirmed in health records, so assessing the burden of specific infections is often done indirectly using time series models using laboratory surveillance datasets[7].

Time series models show that influenza epidemics are associated with cardiovascular mortality in temperate, subtropical and tropical climates[8-10]. UK studies have attributed a substantial burden of hospitalisations and deaths in older adults to both influenza and RSV[11, 12]. Seasonal all-cause mortality in the elderly has been attributed to multiple viruses including influenza, parainfluenza, RSV and norovirus. Estimates from a Dutch study suggest that these viruses account for 6.8% of deaths in people aged ≥85 years, 4.4% in those aged 75-84 years and 1.4% in people aged 65-74 years[13]. However, few studies examine the effects of a comprehensive range of respiratory viruses on specific cardiovascular end-points. Such studies are needed to inform vaccination, antiviral and anti-thrombotic strategies for high-risk patients and for health service planning, especially in settings with limited healthcare infrastructure[14].

In this ecological study we aimed to describe the temporal associations between different laboratory-confirmed respiratory viruses and hospital admissions for MI and stroke using laboratory-confirmed respiratory infections.
Methods

We undertook a time-series analysis of English national aggregated data on hospital admissions for MI and stroke (stratified by age: 45-64, 65-74 and 75+ years), laboratory-confirmed viral respiratory infections and environmental data for the period 1st April 2004 to 31st March 2015.

Cardiovascular outcomes

Counts of MI and stroke-associated admissions to English hospitals aggregated by week of admission (compatible with influenza surveillance weeks) and age were obtained from Hospital Episodes Statistics (HES) via NHS Digital.

MI and stroke events occurring in individuals aged 45 years and over were identified in HES data through records of the diagnosis at hospital discharge and classified according to International Classification of Diseases Tenth Revision (ICD-10 codes for acute MI; I21 and I23, or stroke comprising; ischaemic stroke; I63, or haemorrhagic stroke reflecting intra-cerebral haemorrhage; I61 or sub-arachnoid haemorrhage; I60. We examined the impact of stratifying analyses for stroke admissions into ischaemic versus haemorrhagic types. The date of admission was taken as the date of the vascular event.

Respiratory infections

Counts of respiratory viruses (influenza, parainfluenza, rhinovirus, respiratory syncytial virus (RSV), adenovirus or human meta-pneumovirus (HMPV)) aggregated by week of sample collection for people of all ages were obtained from LabBase[15], which captures all positive test results (i.e. confirmed infections, hence no denominator data are available) reported by hospital laboratories in England. We included all respiratory samples, thus excluding test results (e.g. gastrointestinal samples relating to adenovirus) that are not indicative of ARI. Samples submitted to LabBase come
from both primary and secondary healthcare settings. HMPV appeared to be incompletely reported for early time points, thus data for this virus was examined only for 2010 onwards.

Environmental data

British Atmospheric Data Centre data on daily temperatures (minimum, mean, and maximum) in central England (approximately bordered by Bristol, Lancashire, and London) were obtained and aggregated by week. The MIDAS Land Surface Observation Stations dataset was used to obtain daily data on relative humidity across England, from which absolute humidity was estimated and aggregated by week[16].

Statistical analysis

Weekly counts of MI or stroke admissions (the primary outcomes) were modelled using Poisson regression with a scale parameter set to the Pearson χ2 statistic divided by the residual degrees of freedom to model over-dispersion. Weekly counts of each virus were separately investigated as predictors in models incorporating long-term and seasonal variation as well as environmental data as covariates. We tested four approaches to modelling seasonal variation in MI and stroke; i) categorical calendar quarter (i.e. 4 quarters x11 years), ii) month, iii) Fourier-terms (plus a linear term for year) or iv) 4-knot natural splines. We then used Akaike’s Information Criterion (AIC) to select the final modelling approach. Similarly, AIC guided the multivariable modelling strategy with either natural 3-knot cubic splines or deciles to capture weekly temperature and absolute humidity. Lags of ±3 weeks between the exposure and outcome were investigated to accommodate potential delays between ARI and subsequent complications, including vascular events (e.g. lags of 0 to +3 weeks[3, 5]), and because laboratory surveillance is assumed to reflect respiratory illness presenting in the community at an earlier time point (e.g. lag=-2 weeks).

Results are presented as an incidence rate ratio (IRR) and corresponding 95% confidence interval (CI). The partial autocorrelation function for each model was investigated for evidence of residual
autocorrelation, and where indicated, an additional lag term included in the final model. The proportion of MI or stroke events attributed to each virus was estimated by predicting the number of events under the final model ($X$) and under a model assuming zero circulating virus ($Y$) as $(X - Y)/X$. We re-estimated this value for weeks where levels of circulating virus were high ($\geq$90th percentile of weekly viral counts).

**Sensitivity analyses**

We also examined the impact of excluding data for weeks prior to 2010 (approximately half the study period) because of concerns that health seeking behaviour and surveillance practices changed during and after the start of the 2009 influenza pandemic. Finally, we examined whether restricting viral respiratory infections to people aged 45+ years substantially altered the interpretation of our results.

**Results**

Weekly counts of hospital admissions for MI averaged 476 per week (IQR 429-553) for adults aged 45-64 years, 361 (IQR 318-416) in 65-74 years and 513 (IQR 443-583) in 75+ years (Table 1). The equivalent figures for stroke were 302 (IQR 264-352), 303 (IQR 264-354) and 564 (IQR 496-682), respectively (Table 1).

There were strong temporal shifts in the frequency of MI and stroke, particularly for MI in 2012, which coincides with the introduction of the third universal definition of MI reflecting the development of more sensitive assays for myocardial necrosis[17]. There was evidence of a winter peak for both MI and stroke, particularly within the 75+ age group (Figure 1).

Weekly counts of all respiratory viruses in all ages are outlined in Figure 2 and Table 1, and range from a median of 11 cases per week (IQR 5-53) for influenza to 55 (IQR 7-127) for rhinovirus. Strong
seasonal patterns with large fluctuations in weekly counts were evident for different viruses, particularly for RSV (IQR 9-171).

Environmental data suggested minimum, mean and maximum weekly temperatures of 6.6 (IQR 3.1-10.5), 10.3 (IQR 6.5-14.4) and 14.2 (IQR 9.6-18.6) degrees Celsius. Average weekly absolute humidity was 7.6 (IQR 6.3-9.6) grams per cubic metre.

**Association between MI admissions and viral respiratory infection**

The final multivariable models incorporated calendar quarter of MI admission, and deciles of maximum temperature and mean absolute humidity. In the adjusted models there was no evidence of an association between weekly counts of MI for people aged 45-64 years and any of the respiratory viruses; p>0.1 for all models. For MI in people aged 65-74 years there were small but statistically significant positive associations with weekly counts of adenovirus (IRR 1.00091 (95% CI; 1.00029-1.00153)), rhinovirus (1.00029 (1.00009-1.00048)) and RSV (1.00009 (1.00006-1.00013)): the best fitting models were lagged by 3 weeks (Table 2). There was no evidence of an association between weekly infections with influenza, parainfluenza or HMPV and MI admissions aged 65-74 years. In the 75+ age group associations remained similar to the 65-74 year age group for adenovirus, rhinovirus and RSV (Table 2). However, additional associations were evident for influenza (1.00006 (1.00003-1.00009)) and HMPV (1.00146 (1.00096-1.00196)). Respiratory infection remained significant for influenza or HMPV in all models with lags of ±2 weeks, with the best fitting models having 0-1 week lags.

**Association between all stroke admissions and viral respiratory infection**

As with MI, the final multivariable models incorporated calendar quarter of stroke admission, and deciles of maximum temperature and mean absolutely humidity. In the adjusted models there was no evidence of an association between weekly counts of any respiratory virus and stroke in people aged 45-64 years or 65-74 years; p>0.1 for all models. Weekly counts of RSV (IRR 1.00005 (95%
CI;1.00002-1.00007)) and HMPV (1.000863 (1.00042-1.00131)) were positively associated with counts of stroke admissions aged 75+ years in models with lags of ±2 weeks, with the best fitting models having 1-3 week lags (Table 2). There was no evidence of an association between weekly counts of stroke aged 75+ years and viral respiratory infection in the final models (those with the lowest AIC) for adenovirus, influenza, parainfluenza or rhinovirus. In models with higher AICs (data not shown) there was evidence of a positive association between stroke admissions aged 75+ years and both influenza and rhinovirus infections, with lags of 1-2 weeks.

Stratifying stroke admissions into ischaemic and haemorrhagic types

Ischaemic stroke accounted for 61%, 75% and 81% of all stroke admissions in people aged 45-64, 65-74 and 75+ years, respectively. Results for ischaemic stroke in the 75+ year age group closely mirrored those for MI, with small but significant positive associations identified for adenovirus (IRR 1.000749 (95% CI;1.000237-1.001261)), rhinovirus (1.000345 (1.000181-1.000509)), RSV (1.000064 (1.000036-1.000092)), influenza (1.000051 (1.000027-1.000075)) and HMPV (1.000671 (1.000232-1.00111)) (Table 2). There was no evidence of an association between respiratory virus infection and ischaemic stroke in people aged 45-64, or 65-74 years, or with haemorrhagic stroke in any age group.

Proportion of events attributable to viral respiratory infection

The proportion of events attributable to viral respiratory infection is outlined in Table 3. Figures 3-6 outline the observed and estimated weekly number of admissions attributable to viral respiratory infection for MI aged 65-74 (Figures 3) and 75+ years (Figure 4), and for all (Figure 5) and ischaemic (Figure 6) stroke admissions aged 75+ years. Across the whole study period the proportion of MI admissions in people aged 65-74 years attributable to each virus was 1.4% for RSV, 2.0% for rhinovirus and 2.6% for adenovirus. When restricted to weeks with a high burden of respiratory infection the proportion of MI admissions attributable to infection increased to 6.3-6.9%. Infection-
attributable MI admissions were similar in the over 75s, namely 1.6% for RSV and 2.6% (each) for adenovirus and rhinovirus across the whole study period. Among high virus burden weeks the proportion of MI admissions attributable to infection were 6.6-7.6%. In addition, the proportion of MI admissions aged 75+ years attributable to each respiratory virus was 3.0% for HMPV and 0.4% for influenza, and increased to 2.8%-9.2% when restricted to weeks with high virus burden. The proportion of all stroke admissions aged 75+ years attributable to infection was 0.7% for RSV and 1.7% for HMPV: these estimates increased to 4.1%-5.4% for weeks with high virus burden. The proportion of ischaemic stroke admissions attributable to each respiratory virus was 0.4% (influenza), 1.0% (RSV), 2.3% (adenovirus) and 2.9% (rhinovirus) and increased to 2.6-7.7% when restricted to weeks with high virus burden (Table 3).

Sensitivity analyses

All associations between virus-specific counts of infection and MI or stroke admissions identified previously remained statistically significant after restricting data to time-points after 2010. However, the proportion of admissions attributable to infection was higher relative to the whole time period (Table 3).

Restricting counts of weekly reports of viral respiratory infection to people aged 45+ years did not meaningfully alter the associations reported previously for MI or stroke in people aged 45-64 and 75+ years. However, for people aged 65-74 years the association with MI remained for RSV, but was no longer significantly associated with adenovirus and rhinovirus infections.

Discussion

We examined temporal associations between weekly numbers of MI or stroke admissions and laboratory-confirmed viral respiratory infections. Our results show that, after controlling for environmental factors and long term trends in admissions, higher circulating levels of some respiratory viruses coincide with increased MI and stroke admissions in older people. Specifically, MI
and ischaemic stroke admissions aged 75+ were associated with adenovirus, rhinovirus, RSV, influenza and HMPV. MI admissions in the 65-74 year age group were associated with adenovirus, rhinovirus and RSV, and haemorrhagic stroke admissions were not associated with respiratory infections for any age group. For the full study period, we estimate that a small but significant proportion of MI (0.4%-3.0%) and ischaemic stroke (0.4%-2.9%) admissions in the elderly may be attributable to viral infection, with increased burden during weeks with high levels of reported respiratory infections (up to 7.7%). Conversely, we did not identify evidence of an association between circulating levels of any respiratory viruses and MI or stroke admissions in people aged under 65 years.

Our results add to a growing body of evidence supporting a link between respiratory infection and acute ischaemic events[5, 10, 18-25]. In accordance with other studies we found that a small but significant proportion of ischaemic event admissions among older adults may be attributable to influenza infection[5, 22, 26]. To the best of our knowledge, this is the first study examining the association between acute vascular events and a broad array of common respiratory viruses. Our results provide new evidence that the temporal association between ischaemic vascular events and respiratory infection is not unique to influenza virus, but more widely to rhinovirus, adenovirus, RSV and HMPV, which have similar clinical presentations[27]. By contrast, our results did not indicate an association between parainfluenza and ischaemic vascular admissions in any age group. This finding may reflect a true lack of association or limited statistical power, or differences in seasonality between MI and parainfluenza type 3 (the major circulating type for England), which has a spring/summer peak[28]. Our results for stroke admissions differ to a Canadian time series study that identified positive associations between weekly ARI consultations with both haemorrhagic (1-3 weeks lag period) and ischaemic stroke (16 week lag period) admissions[29]. However, the age groups, lag periods investigated and local seasonality of infection are not directly comparable between the studies. 
Several mechanisms are thought to link infection and acute vascular events, including release of pro-inflammatory cytokines, disruption of atherosclerotic plaques and physiological impacts on heart rate and vasoconstriction[30]. However, much of this evidence examines thrombotic events, with less consistent evidence for haemorrhagic events[29, 31-35]. A higher prevalence of pre-existing cardiovascular and chronic conditions such as cancers, inflammatory and respiratory diseases in the elderly is likely to underpin the greater risk of infection-triggered events in this group[36-38]. Due to the ecological nature of our study we were unable to examine the impact of such comorbidities and other confounders (such as influenza vaccination[24] or treatment with antivirals[39]) that are likely to mediate the risk of vascular events through infection.

Our study is the first in England to investigate acute vascular events attributable to a broad array of viruses (adenovirus, HMPV, parainfluenza, rhinovirus, influenza and RSV). The main strength of this study is the use of laboratory-confirmed infections with national coverage, over an 11 year period, and addressing confounding by environmental factors. The key limitation is the use of ecological methods, which cannot infer causality. However, these methods were well suited to the research question and data sources: the specificity of respiratory infections reported via this national surveillance scheme is likely to exceed 90%[36]. In contrast, counts of ARI will be underestimated due to lower sensitivity of testing (e.g. 47-80%)[36] and highly incomplete sampling, particularly of community settings. Likewise, we chose to focus on MI and stroke because these have clearer diagnostic criteria than other types of vascular event (e.g. angina) and are thus less prone to misclassification.

Time series methods do not rely on having a high proportion of cases diagnosed provided that the proportion recorded does not vary radically over time. We anticipated that ascertainment of respiratory infections would be higher during the summer wave of the 2009 influenza pandemic (tending to bias our estimate of the true association with hospital admissions towards the null; particularly for influenza (Figure 2)). However, overall, our study results showed similar patterns of
association (but with differences in the magnitude of association) across the whole time period and for time points after 2010, suggesting that changes in testing during and after the pandemic do not substantially impact on the interpretation of our findings. We used AIC as an objective aid for selecting the final analysis models; however, the selection of one process over another remains contested and might influence the results[37].

Our results implicate a wider range of respiratory viruses (RSV, HMPV, influenza, adenovirus and rhinovirus) as potential triggers of ischaemic vascular events in older people, which has important implications for clinical management. Of these viruses, currently only influenza has an effective vaccine available, yet its effectiveness is unfortunately diminished in older age groups. RSV vaccines and antivirals are in development and currently being evaluated in clinical trials. Further evidence is needed on the potential harms and benefits of strategies drawing on antivirals, anti-inflammatory or anti-thrombotic agents, such as low dose aspirin for reducing the risk of vascular events following infection. Such approaches may also lead to better understanding of the underpinning mechanisms.

In the UK, adults below the age of 65 years are not eligible for free influenza vaccination unless they are in a clinical risk group. The absence of an association between respiratory infection and vascular events in people aged 45-64 years therefore lends support to current age and risk factor focused influenza vaccination strategies. Future work should explore pathogen-specific vascular triggers, including bacterial respiratory infection[38, 40-42].

**Conclusions**

We showed small but strongly significant associations between respiratory infection and MI and ischaemic stroke hospitalisations in the elderly. These associations occurred across a range of respiratory viruses (RSV, HMPV, influenza, adenovirus and rhinovirus), thus highlighting the importance of further evaluation of the impact of antivirals, vaccination and antithrombotic agents around the time of infection on cardiovascular outcomes.
NOTES

Acknowledgements

We are very grateful for all hospital laboratories in England who submitted their data to the LabBase data system making it possible for us to conduct this study.

Funding

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Conflicts of interest

There are no conflicts of interest to report.


Table 1: Description of MI and stroke admissions, viral infections and environmental data during the period April 2004 to March 2015

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total</th>
<th>Weekly Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI admissions in 45-64 years</td>
<td>280,890</td>
<td>476 (429-553)</td>
</tr>
<tr>
<td>MI admissions in 65-74 years</td>
<td>209,346</td>
<td>361 (318-416)</td>
</tr>
<tr>
<td>MI admissions in 75+ years</td>
<td>296,261</td>
<td>513 (443-583)</td>
</tr>
<tr>
<td>Total MI admissions in 45+ years</td>
<td>786,497</td>
<td>1347 (1217-1541)</td>
</tr>
<tr>
<td>Stroke admissions in 45-64 years</td>
<td>177,505</td>
<td>302 (264-352)</td>
</tr>
<tr>
<td>Stroke admissions in 65-74 years</td>
<td>178,454</td>
<td>303 (264-354)</td>
</tr>
<tr>
<td>Stroke admissions in 75+ years</td>
<td>337,035</td>
<td>564 (496-682)</td>
</tr>
<tr>
<td>Total Stroke admissions in 45+ years</td>
<td>692,994</td>
<td>1175 (1023-1395)</td>
</tr>
</tbody>
</table>

**Viral infections in all ages**

<table>
<thead>
<tr>
<th>Virus</th>
<th>Count</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus</td>
<td>16,282</td>
<td>23 (11-40)</td>
</tr>
<tr>
<td>Influenza</td>
<td>43,642</td>
<td>11 (5-53)</td>
</tr>
<tr>
<td>HMPV*</td>
<td>5,850</td>
<td>13 (4-29)</td>
</tr>
<tr>
<td>Parainfluenza</td>
<td>17,672</td>
<td>22 (11-53)</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>43,408</td>
<td>55 (7-127)</td>
</tr>
<tr>
<td>RSV</td>
<td>85,639</td>
<td>27 (9-171)</td>
</tr>
</tbody>
</table>

**Environmental data**

<table>
<thead>
<tr>
<th>Environmental parameter</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum temperature (degrees C)</td>
<td>14.2 (9.6-18.6)</td>
</tr>
<tr>
<td>Mean temperature (degrees C)</td>
<td>10.3 (6.5-14.4)</td>
</tr>
<tr>
<td>Minimum temperature (degrees C)</td>
<td>6.6 (3.1-10.5)</td>
</tr>
<tr>
<td>Absolute humidity (g/cubic metre)</td>
<td>7.6 (6.3-9.6)</td>
</tr>
</tbody>
</table>

*Data for January 2010 to March 2010*
Table 2: Associations between MI or stroke admission in the final model for each age group and virus. Models where there was no evidence of an association between respiratory infection and admission are not shown.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Age band</th>
<th>Virus</th>
<th>IRR</th>
<th>95% CI</th>
<th>p value</th>
<th>Lag period</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI admissions</td>
<td>75+</td>
<td>Influenza</td>
<td>1.000056</td>
<td>(1.000027-1.000085)</td>
<td>&lt;0.0001</td>
<td>+1 week lag</td>
</tr>
<tr>
<td></td>
<td>75+</td>
<td>RSV</td>
<td>1.000102</td>
<td>(1.000072-1.000132)</td>
<td>&lt;0.0001</td>
<td>-3 week lag</td>
</tr>
<tr>
<td></td>
<td>75+</td>
<td>adenovirus</td>
<td>1.000948</td>
<td>(1.000371-1.001525)</td>
<td>0.001</td>
<td>-3 week lag</td>
</tr>
<tr>
<td></td>
<td>75+</td>
<td>rhinovirus</td>
<td>1.000354</td>
<td>(1.000168-1.000540)</td>
<td>&lt;0.0001</td>
<td>-2 week lag</td>
</tr>
<tr>
<td></td>
<td>75+</td>
<td>HMPV</td>
<td>1.001460</td>
<td>(1.000964-1.001956)</td>
<td>&lt;0.0001</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>65-74</td>
<td>adenovirus</td>
<td>1.000911</td>
<td>(1.000288-1.001534)</td>
<td>0.004</td>
<td>-3 week lag</td>
</tr>
<tr>
<td></td>
<td>65-74</td>
<td>rhinovirus</td>
<td>1.000285</td>
<td>(1.000090-1.000479)</td>
<td>0.004</td>
<td>-3 week lag</td>
</tr>
<tr>
<td></td>
<td>65-74</td>
<td>RSV</td>
<td>1.000092</td>
<td>(1.000059-1.000125)</td>
<td>&lt;0.0001</td>
<td>-3 week lag</td>
</tr>
<tr>
<td>All stroke admissions</td>
<td>75+</td>
<td>HMPV</td>
<td>1.000863</td>
<td>(1.000420-1.001305)</td>
<td>&lt;0.0001</td>
<td>-1 week lag</td>
</tr>
<tr>
<td></td>
<td>75+</td>
<td>RSV</td>
<td>1.000046</td>
<td>(1.000021-1.000071)</td>
<td>0.002</td>
<td>-3 week lag</td>
</tr>
<tr>
<td>Ischaemic stroke admissions</td>
<td>75+</td>
<td>Influenza</td>
<td>1.000051</td>
<td>(1.000027-1.000075)</td>
<td>&lt;0.0001</td>
<td>-1 week lag</td>
</tr>
<tr>
<td></td>
<td>75+</td>
<td>RSV</td>
<td>1.000064</td>
<td>(1.000036-1.000092)</td>
<td>&lt;0.0001</td>
<td>-3 week lag</td>
</tr>
<tr>
<td></td>
<td>75+</td>
<td>adenovirus</td>
<td>1.000749</td>
<td>(1.000237-1.001261)</td>
<td>0.004</td>
<td>-3 week lag</td>
</tr>
<tr>
<td></td>
<td>75+</td>
<td>rhinovirus</td>
<td>1.000345</td>
<td>(1.000181-1.000509)</td>
<td>&lt;0.0001</td>
<td>-2 week lag</td>
</tr>
<tr>
<td></td>
<td>75+</td>
<td>HMPV</td>
<td>1.000671</td>
<td>(1.000232-1.001110)</td>
<td>0.003</td>
<td>None</td>
</tr>
</tbody>
</table>
Table 3: The proportion of admissions for vascular events attributed to a given viral infection for all weeks in the study period, and restricted to weeks with high (>90th percentile) counts of infection.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Age group*</th>
<th>Virus</th>
<th>Proportion of vascular events attributed to infection</th>
<th>2004-2015</th>
<th>2010-2015</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>All weeks</td>
<td>Weeks with high counts of infection</td>
<td>All weeks</td>
</tr>
<tr>
<td>MI admissions</td>
<td>75+ years</td>
<td>Influenza</td>
<td>0.4%</td>
<td>2.8%</td>
<td>0.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RSV</td>
<td>1.6%</td>
<td>7.6%</td>
<td>2.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>adenovirus</td>
<td>2.6%</td>
<td>6.6%</td>
<td>5.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>rhinovirus</td>
<td>2.6%</td>
<td>7.6%</td>
<td>5.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HMPV**</td>
<td>--</td>
<td>--</td>
<td>3.0%</td>
</tr>
<tr>
<td></td>
<td>65-74 years</td>
<td>adenovirus</td>
<td>2.6%</td>
<td>6.5%</td>
<td>5.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>rhinovirus</td>
<td>2.0%</td>
<td>6.3%</td>
<td>3.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RSV</td>
<td>1.4%</td>
<td>6.9%</td>
<td>1.7%</td>
</tr>
<tr>
<td>All stroke admissions</td>
<td>75+ years</td>
<td>RSV</td>
<td>0.7%</td>
<td>3.5%</td>
<td>0.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HMPV**</td>
<td>--</td>
<td>--</td>
<td>1.7%</td>
</tr>
<tr>
<td>Ischaemic stroke admissions</td>
<td>75+ years</td>
<td>Influenza</td>
<td>0.4%</td>
<td>2.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RSV</td>
<td>1.0%</td>
<td>4.9%</td>
<td>1.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>adenovirus</td>
<td>2.3%</td>
<td>5.3%</td>
<td>3.6%</td>
</tr>
<tr>
<td></td>
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<td>rhinovirus</td>
<td>2.9%</td>
<td>7.7%</td>
<td>4.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HMPV**</td>
<td>--</td>
<td>--</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

*Based on optimal model for each virus

**Data for January 2010 to March 2015
Figure Legends:

**Figure 1:** weekly counts of MI and stroke admissions in England for people aged 45 years and over

**Figure 2:** Weekly counts of laboratory-confirmed respiratory viruses between April 1st 2004 and March 31st 2015.

**Figure 3:** Weekly observed admissions for MI in 65-74 year olds, and the estimated excess admissions attributable to each virus

**Figure 4:** Weekly observed admissions for MI in the over 75 years, and the estimated excess admissions attributable to each virus

**Figure 5:** Weekly observed admissions for stroke in the over 75 years, and the estimated excess admissions attributable to each virus

**Figure 6:** Weekly observed admissions for ischaemic stroke in the over 75 years, and the estimated excess admissions attributable to each virus