A Presumed Infectious Event in England and Wales during 2014 and 2015 Leading to Higher Deaths in those with Neurological and Other Disorders

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Abstract

A recurring series of periods of unexplained higher deaths in those suffering from neurological conditions (Alzheimer’s, Dementia, Parkinson’s etc.) has been previously identified, and the effect of the 2012 event was investigated in some detail.

Since that time, a seemingly similar event occurred in 2014, which exhibited all the characteristics of the previous events, namely, spatial spread of both deaths and medical admissions throughout the UK, deaths and admissions limited to a particular range of conditions, all of which endure for approximately 12 months before abating, and a parallel increase in NHS staff sickness absence - all of which are suggestive of an infectious aetiology. The trend observed at national level is greatly attenuated due to the unique kinetics of sub-national spread and duration of the event; however, despite this limitation a specific increase in neurological and other deaths can likewise be seen during the 2014 event.

The 2014 event mainly initiated during the last half of 2014, and as such, the increased deaths only reflected half of the potential increase, although they were highly statistically significant. As before, the increase in deaths is condition, gender and age specific. In addition to those with existing neurological deaths, increased deaths were observed in those with cancer, congenital and perinatal conditions.

A potential interaction between this agent and an influenza outbreak in January of 2015 appears to have led to additional effects against those with Alzheimer’s and dementia and a period of higher deaths inconsistent with the effects of influenza alone.

The pattern of conditions most affected shows some evidence for common immune function aetiology, and the immune modifying virus cytomegalovirus may be in some way involved in these events, either as cause or via opportunistic reactivation.

Keywords: Alzheimer’s; Dementia; Parkinson’s; Influenza; Cancer; Congenital and perinatal conditions; Disease surveillance; Unusual trends; Gender; Age-standardised death; Demography; The ageing population; Cytomegalovirus

Introduction

In recent years, a series of presumed infectious events have been documented in the UK, in which both deaths and medical admissions simultaneously rise, stay high for around 12 months, and then revert back to the baseline level. Most other health care interventions show a simultaneous change at the onset of these events, including, emergency department attendances and case mix, inpatient admissions, case mix and bed occupancy, GP referral and follow-up ratio in outpatient specialties, and the gender ratio at birth. This behaviour is clearly evident in national, local authority and smaller geographies, occurs across other Western countries, shows evidence for spatial spread between small areas, interferes with the calculation of hospital standardised mortality (HSMR), and increases health care costs [1-42]. Particular diagnoses/conditions are affected, and deaths show a large increase for those suffering from neurological disorders, undergoing cancer treatment, and in several other conditions [1-4,6,11,12,15,17-19,21,25,27,32,39].

It has been proposed that these presumed infectious events may be driving the large and unexplained increase in medical admissions observed over the past two decades, both in the UK and elsewhere in the world [43,44].

Evidence suggests that another of these events occurred in 2014, and had the unique feature of very high spatial synchrony with respect to the spread of death across the UK [31,41]. This study seeks to clarify if the effect against those with neurological conditions was repeated, and if a wider range of conditions were affected.

The 2014 event commenced mid-way through the calendar year, but despite this limitation, evidence for statistically significant increases in particular conditions can be discerned. Evidence for a common immune link will be explored, along with the potential for the involvement of the immune modifying herpes virus, cytomegalovirus (CMV).

Methods

Monthly deaths in England and Wales were obtained from the office for National Statistics (ONS), as were statistics relating to the cause of death in 2013 and 2014. A running 12 month total of deaths were used to demonstrate step-like changes in deaths, and to identify both date of onset and magnitude of the increase in deaths. The point of onset for each step-like increase in deaths was determined by comparing successive 12 month blocks of data. Hence the sum of deaths January 2000 to December 2000 is compared with the sum of deaths January 2001 to December 2001, move forward one month and repeat the comparison. The point of maximum difference identifies the onset of a step-change (up or down).

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The population of England and Wales in 2013 and 2014 by 5 year age band was also obtained from the ONS. The percentage change in the population (relative to 2013), and the adjustment factor applied to 2014 deaths are given in Table 1. Cause of death numbers were adjusted for population (relative to 2013), and the adjustment factor applied to 2014 age band was also obtained from the ONS. The percentage change in the baseline position, and the deviation between the population-adjusted 2014 deaths and 2013 was calculated as a standard deviation (STDEV) equivalent by applying any changes in population age structure between 2014 (adjusted to 2013 equivalent) and 2013, as per Table 1. This is similar to the adjustment applied in the previous study [32].

The difference in deaths was calculated as a standard deviation (STDEV) equivalent using Poisson Statistics. Poisson statistics is directly relevant to integer events, where there is no ambiguity regarding the outcome (dead/alive). By definition, the standard deviation associated with a Poisson distribution is equal to the square root of the average. On this occasion, the deaths in 2013 were chosen as the average or baseline position, and the deviation between the population-adjusted 2014 deaths and 2013 was calculated as a standard deviation (STDEV) equivalent. Any difference greater than 2 standard deviations can be considered to have increasing statistical significance. It is worth noting that in a Poisson distribution 85% of all occurrences occur below +1 STDEV, and 97.7% occur below +2 STDEV, hence +2 STDEV can be considered as close to the 98% confidence interval. Expressing the difference as a STDEV has the advantage of adjusting for the effect of size (via the square root function), however, the raw percentage differences are also show for comparison. Tables S1 and S2 in the supplementary material give full details of both STDEV and percentages differences for all international classification of diseases (ICD) chapters and age bands.

Additional data regarding Alzheimer and dementia deaths during and after an influenza outbreak in January of 2015 was extracted from a report published by the ONS [45].

Results

Saw-tooth behaviour in the trends

There is no demographic reason for deaths in England and Wales to show anything other than a continuous trend to declining deaths in the interval 2010-2015 [23]. However, Figure 1 demonstrates completely abnormal behaviour revealed by the application of a running 12 month total of deaths, and also reveals how calendar year totals can be highly misleading. A full explanation regarding interpreting running 12 month totals is given in the discussion section.

From Figure 1, it can also be seen that the calendar year view of deaths depends greatly on the disposition of December relative to the initiation of the step-like events. This can mask the underlying trends, as can be observed for the calendar years ending Dec-09 and Dec-10.

Of special interest to this study, is the disposition of the 2014 event as seen in the national figures. In England and Wales the 2014 event initiates around Jun-14 (mid-year) and continues through to Jul-15. The total stays high for a few more months due to the small area spread within the two countries and due to an influenza outbreak in January of 2015 (the line labelled ‘Adjusted’ seeks to remove the impact of the January 2015 influenza outbreak from the running 12 month total). However, due to the profiles resulting from the earlier 2012 event, the calendar year total of deaths for 2014 is lower than that for 2013. The impact of sub-national spatial spread on the initiation date for the step-increase in deaths is addressed in a following section.

It has been previously claimed that certain diseases/conditions may be more sensitive to these presumed infectious events than others. Given that 2014 contained a six month period of one of these events, then despite the lower total deaths in 2014 relative to 2013, it would be expected that these sensitive conditions would show a net increase in 2014, despite a prevailing reduction in deaths in the calendar year totals. From the peak in the running total it can be deduced that the agent was absent for 8 of the 12 months in 2013, and hence any comparison against 2013 is a minimum case scenario. Note that the January 2015 influenza outbreak which commences around the second week of January 2015 does not impact on the 2014 total.

This is entirely apposite for the analysis of the cause of death shown in Figure 2. In Figure 2 deaths in 2014 have been adjusted to a 2013 equivalent by applying any changes in population age structure between the two years. The change in population is in fact so small that it makes negligible difference to most age bands except for a 4% increase in the 90+ age groups (Table 1). Figure 2 displays the change in deaths as a standard deviation equivalent (STDEV) difference (Poisson) relative to 2013. This allows the reader to rapidly distinguish changes which are statistically significant (despite an otherwise background reduction in deaths). As can be seen, certain age bands for particular causes of

### Table 1: Difference in population between 2013 and 2014 in England and Wales.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>% Change</th>
<th>Adjusting Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 1</td>
<td>0.4%</td>
<td>0.995642</td>
</tr>
<tr>
<td>1-4</td>
<td>0.4%</td>
<td>0.995642</td>
</tr>
<tr>
<td>5-9</td>
<td>2.6%</td>
<td>0.97443</td>
</tr>
<tr>
<td>10-14</td>
<td>-0.2%</td>
<td>1.001793</td>
</tr>
<tr>
<td>15-19</td>
<td>-0.8%</td>
<td>1.007962</td>
</tr>
<tr>
<td>20-24</td>
<td>0.1%</td>
<td>0.999406</td>
</tr>
<tr>
<td>25-29</td>
<td>0.9%</td>
<td>0.990790</td>
</tr>
<tr>
<td>30-34</td>
<td>0.7%</td>
<td>0.993382</td>
</tr>
<tr>
<td>35-39</td>
<td>0.8%</td>
<td>0.992478</td>
</tr>
<tr>
<td>40-44</td>
<td>-2.3%</td>
<td>1.023103</td>
</tr>
<tr>
<td>45-49</td>
<td>-0.2%</td>
<td>1.002233</td>
</tr>
<tr>
<td>50-54</td>
<td>2.7%</td>
<td>0.973419</td>
</tr>
<tr>
<td>55-59</td>
<td>2.2%</td>
<td>0.978934</td>
</tr>
<tr>
<td>60-64</td>
<td>-0.9%</td>
<td>1.00915</td>
</tr>
<tr>
<td>65-69</td>
<td>1.9%</td>
<td>0.98059</td>
</tr>
<tr>
<td>70-74</td>
<td>3.7%</td>
<td>0.962814</td>
</tr>
<tr>
<td>75-79</td>
<td>2.3%</td>
<td>0.976999</td>
</tr>
<tr>
<td>80-84</td>
<td>1.1%</td>
<td>0.988918</td>
</tr>
<tr>
<td>85-89</td>
<td>2.1%</td>
<td>0.978713</td>
</tr>
<tr>
<td>90-94</td>
<td>4.2%</td>
<td>0.957909</td>
</tr>
<tr>
<td>95+</td>
<td>4.2%</td>
<td>0.957909</td>
</tr>
</tbody>
</table>

death using the ICD chapter summary show significant increases (full
detail covering all ICD chapter, age and gender combinations are given
in Tables S1 and S2 in the supplementary material). Hence there are
statistically significant increases in deaths due to cancers, diseases of
the blood and endocrine systems, persons with congenital conditions
and for mental and behavioural conditions (mainly dementia at 96% of
deaths in this ICD chapter) and neurological conditions (mainly Par-
kinson's and Alzheimer's at 55% of the chapter).

Across multiple conditions those aged 90-94 are particularly affect-
ed, while a significant cluster of conditions in the age band 40-44 are
not, and reflect the general lower deaths in 2014. As has been previously
noted, there are consistent age-specific undulations which are statisti-
cally significant.

Finally, Table 2 summarises those conditions and age groups show-
hing the highest level of statistical significance. This Table is presented
in the hope that retrospective analysis of biopsy material for particular
susceptible groups may be the most likely to contain the agent respon-
sible for this remarkable increase in deaths.

Time series of outbreaks

The 2014 event is part of a longer time series of these presumed in-
fec tious events. Table S3 in the Supplementary material gives details of
all events since 2001 for local government areas in England and Wales
(percentage increase in deaths, etc). Since 2000 these events appear to
occur at roughly two year intervals, however as can be seen in Table S3
they do not appear to occur in all areas during each outbreak (in Table
S3 "n/a" signifies those areas where no apparent event was observed,
while "n/s" signifies increases which are not statistically significant),
with some areas showing higher disposition to this behaviour than oth-
ers. In some years the overall magnitude of the event appears to be far
lower than others, i.e. a median step- increase in deaths of 5% in the
2006 event compared to 8% in the 2012 event. Highest count of loca-
tions with no apparent increase occur in 2002 and 2010, while highest
count of a not statistically significant rise occur in 2006 and 2002, while
the highest count of both occurs in 2006 and 2002.

As has been observed in Figure 1 influenza outbreak in January
2015 can potentially lead to an inflated estimate of the step-change. As
would be expected from the usual rapid spread of an influenza outbreak
every area in England and Wales shows a spike in deaths in January
2015 (which commenced at the start of the second week in January), i.e.
there is very high spatial synchrony. Table S3 therefore contains both
the raw value of the step-increase and an adjusted value. The adjusted
value was obtained by substituting Jan-15 deaths with Dec-14 values
(when influenza was largely absent). While adjustment for the effect of
influenza reduces the value of the apparent step-increase (median val-
ue reduced from 11.4%-9.1%), the 2014 event still achieves the highest
step-increase in deaths since 2001 in the majority of government areas,
and this concurs with the large increase observed in Figure 2 for many
age-condition groups.

Also given in Table S3 is the average number of deaths in each gov-
ernment region (average 2001-2015), the 85% confidence interval (CI)
from Poisson statistics, and an estimate of the slope of the reduction in
total deaths observed in the early years of the time series. Deaths were
reducing in the earlier years due to demographic factors and improving
life expectancy. Due to this reduction estimates for the step-up in the
early years may be an under-estimate. The final columns in Table S3
also give the value of the maximum step-up (at initiation) and the max-
umum step-down (at cessation) for events over the period 2001-2015.
The maximum step-down on cessation of the event being an alternative
estimate of the percentage increase in deaths. Due to this reduction esti-
mates for the step-up in the early years of the time series. Deaths were
also reducing in the earlier years due to demographic factors and improving
life expectancy. Due to this reduction estimates for the step-up in the
early years may be an under-estimate. The final columns in Table S3
do not include the 2014 event.

To further demonstrate the presumed infectious nature of these
events the initiation date for the 2014 event has been given for each
local government area. While initiation clusters around June and July
in 2014, there is a spread of dates from late 2013 through to March
2015, i.e. spatial synchrony is much lower than an influenza-like event.
The same behaviour applies to all previous events. Hence the behaviour
shown in Figure 1 is a composite picture for the whole of England and
Wales.

Effect continues in 2015

To demonstrate that the event continues into 2015 monthly data
from the ONS for Alzheimer and dementia deaths [45] are displayed in

Table 2: Body systems/conditions, gender, and age groups where shifts of high-
est statistical significance (>4 STDEV) indicate greatest likelihood of isolating the
agent.
As can be seen, neurological deaths increase substantially in January 2015 due to an influenza outbreak, however after this they continue to be high until around June 2015 when the national data should show a step-down at the cessation of the event. This step-down can be discerned in the data from July onward, however, recall from Table S3 that the national picture is a composite of spread across the whole of England and Wales and that late spread in some areas will create an additional tail beyond June in Figure 3.

### Did influenza interact with the other agent?

During the January 2015 influenza outbreak there were 11,900 excess deaths compared to December 2014, and 13,800 excess deaths compared to the average for the previous five years [45]. Around 3,000-3,600 of this total were for persons suffering from Alzheimer's and dementia [45], i.e. those with neurological disorders (including Parkinson's, etc) accounted for greater than 25% of the entire deaths.

The age-standardized death rate for those with Alzheimer's and dementia increased 19% in 2015 compared to 2014 [45], although the exact magnitude of this increase depends on the weighting afforded to each age group in the age standardization process, and to the fact that an outbreak of the other agent had occurred six month earlier in 2014. The figure of 19% is therefore probably an underestimate.

The possibility of interaction between influenza and the other agent is revealed in Figure 1 where the ‘Adjusted’ line shows a five month plateau after the point at which the running 12 month total should be showing a ramp-down. Hence we can discern that interactive effects between the suspected infectious agent and influenza seemed to occur over a five month period (January 2015 to May 2015). This seemingly concurs with the downward slope of the Alzheimer’s and dementia line in Figure 3 over this period.

### Discussion

**Running 12 month totals as a diagnostic tool**

Some explanation is required to understand the outcome from a running 12 month chart. In a running 12 month total (as in a calendar year total) the underlying seasonal trend in deaths has been minimised, as has the far higher Poisson scatter associated with the smaller monthly totals. However, a running total is an excellent method for detecting step-like changes in deaths, with the foot of a ramp up marking the initiation of the step-like increase. A disadvantage of a running 12 month total is that it can sometimes create an intellectual challenge for audiences used to interpreting trend lines. This is because the running 12 month total method also transforms the shape of a sudden step-like change in the rate of deaths into a ramp, where the foot of the ramp marks the point of initiation of the step-like increase (or decrease at the cessation of the event). As long as these points are kept in mind Figure 1 is enormously helpful in the context of this study.

Hence in Figure 1, at Jan-10 there are 485,000 deaths during the previous 12 months. Were a step-like increase in deaths to occur, say to 495,000 equivalent per annum, then the running total ending Feb-10 would contain 11 months of 485,000 deaths per annum plus 1 month of 495,000 deaths per annum, i.e. a ramp would ensue whose slope was equal to the step-increase in deaths. If the step-increase endures for 12 months, the ramp will eventually culminate at the new higher level, which can be seen in the Jan-11 peak in Figure 1. When the step-up in deaths ceases, a ramp down then ensues as the higher number of deaths dilutes out of the running 12 month total. Hence the saw-tooth behaviour seen in Figure 1 is a characteristic of this step-up and step-down behaviour. Prior to 2000 these events appeared to occur at roughly twice per decade [23], but since 2000 seem to have shifted to an event every second year. It may be a coincidence, but early in 2000 marked the transition to a 100 year minimum in influenza activity in the UK [6,40,46].

This is not the only event which would lead to higher deaths, and periods of extreme heat or cold or a larger than usual winter infectious event would lead to a temporary spike in deaths-as per the influenza outbreak in January 2015. In a running 12 month total any spike events show themselves as a table-top like feature, i.e. say 10,000 extra deaths which stay in the running total for 12 months. In Figure 1, spike (winter infectious) events in Jan-09 and Jan-15 can be seen to add a table-top like feature on top of a ramp-like feature arising from a genuine step-increase (although additional interactive effects may act to enhance the table-top feature in the trends). The impact of such spike events can be adjusted as per that for the January 2015 influenza outbreak presented in Figure 1.

### Choice of the statistical method

The relatively slow spread of the agent coupled with an approximate 12 month duration for the effects upon deaths and admissions, and the resulting attenuation of any apparent effect in larger geographies [47-53], probably explains why these events have gone unnoticed for such a long time. For example, the preceding 2012 event saw initiation of the step-increase in deaths in 75% of English and Welsh local authorities after January 2012, in 50% after April 2012 and in 25% after August 2012. This staggered spread explains why the effects against neurological and other deaths were high in both 2012 and 2013, as noted in the previous study [32]. Hence the number of deaths in 2013 (the reference year in this study), are already elevated against the true 'average' number of deaths, were the agent to be genuinely absent throughout the entire calendar year.

Under normal circumstances, allowance is made in the calculated difference from the average for Poisson variation in both the average, and in the difference to be evaluated. However, since the only available estimate for the ‘average’ is already inflated by greater than 3.3% (as in Figure 1) against the minimum case position occurring for the...
12 months ending May 2014, it is safe to omit the normal variation in the 'average', and instead calculate the difference as standard deviations equivalent. In addition, it has already been pointed out that use of 2014 calendar year deaths is also a 5.6% underestimate of the maximum effect of the 2014 event which occurs for the 12 months ending July 2015. No attempt has therefore been made to calculate the usual statistical tests since the simple calculation of standard deviations difference is satisfactory for demonstrating that a significant change has occurred despite considerable under-estimation of the true magnitude of the effect.

Are the events due to an infectious agent?

At the commencement of any discovery the researcher has to present the statistical evidence to support the proposed modus operandi. Further studies are then conducted to confirm or disprove the initial hypothesis. A summary of the statistical evidence supporting an infectious source will now be given:

1. In the UK these events have been documented back to the 1950's via their effect upon deaths [23], and back to the 1960's in the US via their effect upon total health care costs [6,26].
2. Each event exhibits spatial spread throughout the UK, and more widely in other Western countries so far studied [23-26,29-31,35]. Such international spread is consistent with the spread of pathogens via high-volume air travel [47-49].
3. A number of small-area studies involving the 2008, 2010 and 2012 events have established typical granularity/heterogeneity effects, both in terms of date of onset, and magnitude of the effect against medical admissions to hospital, and against deaths [23-26,29-31,33-34,39,50].
4. The events are seemingly inextricably linked to the totally unexplained rise in medical admissions observed over the past three decades [43,44].
5. Both the increase in deaths and medical admissions are restricted to a limited range of conditions/diagnoses which are sensitive to immune manipulation/disturbance via sensitivity to infection, inflammation and auto-immunity [6,34,51].
6. Climatic and environmental causes such as temperature, pollution, noise, etc, can be excluded due to the observation that immediately adjacent very small areas can initiate at different times and show wide variation in the magnitude of the increase in deaths and/or medical admissions [33,39,50].
7. The events are accompanied by a parallel rise in (and spatial spread of) sickness absence, as measured by statistical returns submitted by NHS organisations [31,52].
8. An accompanying change in the gender ratio at birth points to a more widespread population effect [8].
9. In earlier years the events appeared to occur about twice per decade, but switched to three per decade in the 1990's, and to every second year since 2000 [23,31,42,50].
10. The statistical evidence seems to indicate all the classic signs expected from a genuine infectious event, namely, granularity/ heterogeneity, synchrony, and a related set of diagnoses/conditions associated with each event.

Magnitude of the effect

Whatever is behind these presumed infectious events is clearly a capable agent/pathogen. The huge divergence between the ONS 2008-based forecast and actual deaths in Figure 1 are a testament to the sheer power of this agent, and its ability to modify the trajectory of death within a nation (as per Table S3). In this respect, note that following the cessation of the 2008 and 2010 events, deaths almost revert back to the ONS forecast, however, both the 2012 and larger 2014 event take the trend further and further away from the ONS forecast.

It is of interest to note that there is increasing evidence that the initiation of a step-like increase in deaths occurring prior to the winter can lead to a magnified effect in any ensuing winter infectious events, presumably due to interaction with particular winter viruses/strains [40]. In particular, the large 2014 event plus an influenza outbreak in January 2015 led to a very large increase in excess winter mortality (EWM) during the winter of 2014/15, to the extent that EWM was the highest since the winter of 1999/00 [54]-the last instance of a large influenza outbreak in the UK. The 2009 'swine flu' pandemic did not have a large effect upon deaths since it mainly affected the younger age groups.

Several studies have demonstrated that greater than 300% increases in deaths are achieved in very small areas approximating to a social network (with an average of 1 death per annum) [35,50]. Complex spread of the agent leads to step-up and step-down cancelling one another out, with resulting profound attenuation of the apparent effect observed at national level [53].

The 2010 event seen in Figure 1 is an excellent example of this attenuated effect. It is now known that the 2010 event represented a case of very slow spread of the agent, i.e. low synchrony, and in the local authority area of Wigan on the outskirts of Greater Manchester, spread through every small area (or social network) took a full two years to occur [33]. In complete contrast, the 2014 event appears to have displayed the highest level of synchronous spread so far observed for this agent. Synchrony was so high that over 60% of local authority areas experienced the highest apparent step-increase since 2001, and that the majority of initiation across England and Wales occurred within a 6 month window (May to October) during the summer of 2014 [31,41]. Summer initiation tends to preclude the majority of winter infectious agents as a potential source.

The earlier study (in this journal) on neurological deaths associated with these events compared 2012 and 2013 calendar years against 2011 [32]. The disposition of the 2012 event in terms of its effect upon the 2012 and 2013 calendar year totals in Figure 1 confirms that this was a valid analytical approach. This study has attempted a far more challenging goal of demonstrating that an increase in deaths for susceptible conditions should lie hidden in 2014 versus 2013 data despite only 6 months of infectious presence in 2014. This appears to have been successfully achieved.

Age-gender specific profiles

As was previously demonstrated, persons with existing neurological conditions are most susceptible to the agent, however in an age- and gender-dependant manner [17,32]. The immune priming effects of repeated exposure to different strains of the same agent, which creates saw-tooth patterns in age-related susceptibility to the next strain, may well be the most likely explanation for this behaviour [55]. Indeed these events are known to be characterised by single-year-of-age specific patterns in both medical admissions and deaths [18,19,24-25,33,39].

While females have a generally higher disposition to death and admission during these events [26], it is interesting to note that the gender specificity is both condition and age-specific. Clearly whatever is
involved, has a complex web of probable immune dysregulations and counter balances.

**Neurologic conditions, inflammation and infection**

In England, those suffering from Alzheimer’s and dementia are known to account for around 30% of excess winter mortality, range 12%-43% depending on the year [56]. Hence, as a group they are clearly susceptible to ‘winter’ environmental and infectious stress in general. Part of this susceptibility lies in the observation that those with neurological disorders are also characterised by inflammatory processes, leading to a higher risk of becoming bedridden and the consequent effects thereof [17]. There is now an abundance of evidence to show that those with neurological conditions experience higher levels of background inflammation [57, 58], thereby making them more susceptible to any agent taking opportunistic advantage of this situation. Hence, the higher deaths following the 2014 outbreak of the agent, and the augmented effect of the January 2015 influenza outbreak.

**Is cytomegalovirus involved?**

The potential involvement of the immune manipulating herpes virus, cytomegalovirus (CMV) has been suggested to occur in these events. The evidence for the potential involvement of CMV can be summarised as follows:

1. CMV is the largest herpes virus and possesses a formidable array of immune modulating genes. Its genetic potential is further enhanced by mid-frame and reverse frame transcription, along with resident RNAs within the viral capsule [34]. Very high mutational potential exists in most of the DNA except for that part devoted to replication [34].

2. In large population studies, CMV is known to increase the risk of death in those conditions associated with these events. This is especially the case for around 20% of the population having elevated anti-CMV IgG [34, 59].

3. The medical conditions which show an increase in admissions during these events (at roughly 10 additional admissions per additional death) [28], appear to have the same range as is observed for acute admission for CMV-disease [6, 34]. However it is suspected that the real cause for the increased admissions lies in the more subtle sub-clinical immune-manipulation by CMV rather than in overt ‘acute’ CMV-disease.

4. CMV is now known to exert immune modulating effects even in a state of dormancy [60-64].

5. Finally, infection of neurological tissues are very common with CMV [59], and appear to occur during these events [6].

Indeed just a few publications from early 2016 suggest that CMV is involved in the development of long-term conditions such as autoimmune disease (via a CMV peptide-specific antibody altering NK cell homeostasis) [65]; in increased risk of hypertension (79% of hypertensive patients were CMV +ve which was 1.4-times higher than controls-although race and gender seems to play a role) [66]; the presence of CMV DNA, RNA and proteins in cases of alveolar soft part sarcoma [67], which are part of a growing list of oncomodulatory and oncogenic roles for this virus [34]; CMV-related hospitalization in inflammatory bowel disease is associated with a 7.1 (OR) for in-hospital death, a 7.8 day longer hospital stay and $66,500 higher hospital costs [68]; increased risk of high systolic blood pressure (a marker for atherosclerosis) especially in older women not taking anti-hypertensive medication (this effect was independent of CMV IgG status indicating sub-clinical effects probably mediated by CMV in latency) [69]; and a statistically significant association between CMV and metabolic dysfunction in non-obese adults [70]. One crucial study has demonstrated that CMV viral load in the blood monocytes and anti-CMV IgG levels of healthy persons suddenly jumps around age 70 [71], where some 70% of male and 82% of female deaths in England and Wales occur above the age of 70. This is clearly a capable pathogen even among the so-called immunocompetent population [6, 59].

The inclusion of persons undergoing cancer treatment in Figure 2 and Table 2 as a susceptible group, confirms earlier studies. During the 2008 event, it was observed that patients admitted to hospital with a cancer diagnosis showed characteristic higher deaths relative to 2007 [3, 4]. It was proposed that re-infection/activation with CMV was a potential explanation for this behaviour. Another study noted that the incidence of particular cancers in the US also appears to rise and fall with the onset of these events [1]. These cancers are seemingly those most susceptible to the oncogenic and oncomodulatory effects of CMV [34].

An interesting insight into potential Alzheimer/cancer effects during these outbreaks lies in the recognised inverse association between Alzheimer’s and cancer [72-75]. A recent study on the age-related effects of the outbreaks has also identified an inverse relationship between medical admissions and cancer admissions, in that cancer admissions show the greatest rise in those ages where medical admissions show the least and vice versa [44]. Febrile conditions may alter the function of Pin1 (a cis-trans isomerase altering proteins and facilitating signalling in diverse pathways) such that cancer risk is diminished and Alzheimer risk is increased [72].

The issue of CMV is even more eapposite, in that persons with congenital conditions also appear in Figure 2 and Table 2. It is well known that CMV is responsible for around 40% of congenital conditions and that a large proportion of these have a neurological basis [76-78]. A significant proportion of these persons will have had lifelong exposure to the immune erosive effects of CMV; however, this does not prove that CMV is the actual agent. In the presence of other agents, such as HIV/AIDS, CMV is known to take opportunistic advantage, and impose a degree of CMV-specific patterns of disease on top of conditions emanating from the other agent [79-81]. It is now known that CMV can exert its immune modulating effects even during latent infection [60-64].

The other conditions in Table 2 can likewise be said to be CMV-susceptible, in that CMV is known to be active in disease expression in these body systems [59]. Interestingly the wobble in the gender ratio at birth which accompanies these events is consistent with the known deleterious effect of CMV as a risk factor for spontaneous abortion [82], and abnormality-associated infection targeted especially against the female foetus [83].

Lastly, in CMV seropositive Alzheimer’s patients, CMV acts as a promoter of an increased inflammatory response with higher levels of TNF-γ secretion (and possibly also IL-1B) by peripheral blood mononuclear cells after anti-CD3/CD8 or CMV pp65 stimulation [84]. This effect was specific to CMV positive and demented Alzheimer’s patients. In another study CMV infection increased the risk of Alzheimer’s by 2.2 fold (RR) and was associated with a faster rate of cognitive decline [85]. In accord with the known higher susceptibility of black persons to Alzheimer’s levels of CMV IgG were around 1.2-times higher in black versus white age matched individuals [85]. In Parkinson’s disease those who are CMV +ve have higher frequency of myeloid DCs with a pro-inflammatory phenotype [86]. A possible role for CMV may lie
in its ability to interfere with the ubiquitin proteasome system (UPS), which among other functions, acts to clear aggregated amyloid [87].

Respiratory infection hospitalization among children with neurological conditions are around 5-7 times higher, rising to 14.5 times higher aged 10-18 [88]. Respiratory admissions are known to rise during these outbreaks [21]. The above would accord with the proposal that CMV is somehow involved in these presumed infectious events.

While agents such as herpes simplex virus (HSV1) and Chlamydia pneumoniae may be the primary infectious agents initiating Alzheimer’s [89], it is important to realise that the action of many pathogens may be enhanced by the immune modifying effects of existing CMV infection [34,90]. Similarly a review of the role of CMV in autoimmunity concluded that although other viruses may be more potent at initiating autoimmunity, CMV was probably acting to enhance resulting symptom severity and disease progression [51]. This also accords with the central role of CMV in the role of the ‘infectious/pathogen burden’.

Pathogen burden is the study of the role of multiple pathogens in symptom severity and disease progression [22,34,90-97]. Pathogen burden has also been implicated in the progression of Alzheimer’s [98], dementia [95-97], and Parkinson’s [99]. CMV is highly likely (via its orchestrating role) to be acting to enhance symptom severity and disease progression as in autoimmunity. In this respect, in elderly persons high CMV IgG is associated with monocyte activation, polyfunctional- and expression of inflammatory cytokines which are associated with functional and cognitive decline [100].

**Interaction with influenza**

Interactive effects between the agent and influenza appear to have been identified in Figure 3. Given the potential involvement of CMV it is of interest to note that CMV interferes with influenza immunity and vaccine effectiveness [34]. All major studies on influenza vaccine effectiveness conducted to date have ignored the effects of CMV and/or this other agent [101]. We need to ask the question as to exactly how much antigenic drift per se contributes to the lower vaccine effectiveness observed in some years [101], as opposed to the contribution from CMV and/or the other agent?

A potential interaction between an outbreak of the proposed agent and the World War I ‘Spanish flu’ outbreak has been recently suggested [44]. There is preliminary evidence that the interaction between the agent and influenza has triggered a 2015 ‘outbreak’ commencing around May since emergency admissions in England underwent another step-like increase at that point (unpublished).

**An approximate 12 month duration**

Some comments regarding the approximate 12 month duration of the presumed infection are required. While it is already recognised that infectious outbreaks can display a wide range of kinetic forms depending on the speed and mode of transmission [68], the apparent duration for 12 months is a novel feature of these events. It would appear that initiation of an event leads to a time cascade of disease resulting in both hospital admissions and death [6,13,15,19,25,39]. The first to be admitted are those with vague or unspecified viral illness, then pneumonitis and other diseases dependent on immune dysregulation via inflammation [19,25]. My own preliminary study of patients admitted to intensive care during these outbreaks shows that inflammatory markers are elevated during the first 6 months of the event, i.e. not everything persists for the 12 months. The suspicion is that the 12 month duration is itself a composite of conditions, each with its own time trajectory. However, for reasons specific to the agent, the bulk of the observable effects on medical admissions and deaths appear to wane after around 12 months. The more aggressive forms of tuberculosis may show a 2-3 year lag after these events [13], and there is preliminary evidence that the increases in certain types of allergy admissions during these events occur earlier than others [20]. This agent seemingly instigates complex cascades of disease, presumably due to immune dysfunction.

This study seems to have inadvertently characterised diseases/conditions which show a strong response during the first half of the event/outbreak. Future research will need to use running 12 month totals for each condition and to compare these to the trend in total deaths to determine the time-sensitivity of each condition.

**Future research**

Research relating to the spatial spread of this agent clearly indicates that the effect observed for England and Wales is a composite picture of small area spread [2,9,19,29-31,33,39,50]. By implication, sophisticated small-area spatial analysis is required to amplify the ‘signal’ [53]. The small area studies have also highlighted the possibility that unique single-year-of-age/gender interactions may be occurring [18,19,24,39]. Preliminary research using small area data seems to indicate that male/female initiation often shows lags, presumably due to slightly different routes to infection, and the chance events initiating an infectious surge (unpublished). While this accords with the known behaviour of CMV [6,34], additional research is required to confirm the true agent or trigger initiating these events.

**Conclusions**

The effect of the 2014 event, which initiated toward the second half of the calendar year, did indeed lead to increased deaths in persons suffering from a range of susceptible conditions, most notably for neurological conditions. This increase in death was expressed despite lower total deaths in 2014 compared to 2013. This overall difference in total deaths arose as an artefact of calendar year reporting of deaths relative to the rise and fall in deaths instigated by these events.

It remains to be determined if the agent responsible for these outbreaks is itself a cause of neurological conditions. However it is becoming increasingly clear that CMV is in some way associated with these events. Interestingly a recent study has confirmed that CMV infection leads to a higher risk of developing Alzheimer’s (RR=2.15) [85]. The observation regarding immune manipulation by CMV while latent is relevant [60-64]. The wider possibility of the involvement of CMV has been discussed elsewhere [6,34,90], and its role in the expression of the pathogen burden is also highly relevant.

The full extent of the effects of this agent will only be established once the 2015 calendar year data (for cause of death), is released by the ONS sometime in late 2016. Indeed it has now become public knowledge that the 2015 calendar year showed the highest increase in deaths in nearly 50 years [45]. This only confirms the events noted in Figure 1. However, researchers around the world need to be alert to the presence of this agent, and those wishing to conduct retrospective analysis of blood and other tissue samples can concentrate their efforts according to the age/condition combinations highlighted in Table 2. However, as has been demonstrated in Table S3 (Supplementary material) the relatively slow spread across the UK implies timing differences between locations and these needs to be confirmed in any retrospective analysis of tissue/blood samples.

As an interesting aside, it is curious that UK government agencies...
appear to wish to support the notion that whatever is happening can be explained by reference to existing phenomenon [10,45,102]—despite ample evidence to the contrary. However, attention needs to now turn to isolating the exact agent responsible for the events. In the early days of HIV/AIDS research CMV was suspected as a potential pathogen, however, it is now known that CMV was merely taking opportunistic advantage of the immune impairments arising from HIV infection [79-81]. It is possible that once again CMV is waving a red flag to alert us to the potential presence of another more serious pathogen or alternatively to a role for CMV-mediated pathogen burden.

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References


