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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.

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e population of England and Wales in 2013 and 2014 by 5 year age band was also obtained from the ONS. e 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 change to give a population-adjusted di erence in deaths between 2014 (adjusted to 2013 equivalent) and 2013, as per Table 1. is is similar to the adjustment applied in the previous study [32].

e di erence 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 de nition, 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 di erence greater than 2 standard deviations can be considered to have increasing statistical signi cance. 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% con dence interval. Expressing the difference as a STDEV has the advantage of adjusting for the e ect of size (via the square root function), however, the raw percentage di erences are also show for comparison. Tables S1 and S2 in the supplementary material give full details of both STDEV and percentages di erences for all internelevanaal gbor

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. is 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 gures. In England and Wales the 2014 event initiates around Jun-14 (mid-year) and continues through to Jul-15. e total stays high for a few more months due to the small area spread within the two countries and due to an in uenza outbreak in January of 2015 (the line labelled 'Adjusted' seeks to remove the impact of the January 2015 in uenza outbreak from the running 12 month total). However, due to the pro les resulting from the earlier 2012 event, the calendar year total of deaths for 2014 is lower than that for 2013. e 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 in uenza outbreak which commences around the second week of January 2015 does not impact on the 2014 total.

is 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. e change in population is in fact so small that it makes negligible di erence 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) di erence (Poisson) relative to 2013. is allows the reader to rapidly distinguish changes which are statistically signi cant (despite an otherwise background reduction in deaths). As can be seen, certain age bands for particular causes of

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. is 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 c9(m)19(p)]TJ16(s lo)[5(r)13(en)Thas-6(h)4(o)-2e ra(e)]TJ0.0t rat ig

Figure 3. ere were three changes in how neurological disorders were coded and counted in the previous ve years data, for which the ONS has made a retrospective adjustment.

As can be seen, neurological deaths increase substantially in January 2015 due to an in uenza outbreak, however a er 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. is 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.

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During the January 2015 in uenza outbreak there were 11,900 excess deaths compared to December 2014, and 13,800 excess deaths compared to the average for the previous ve years [45]. Around 3,000-3,600 of this total were for persons su ering 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.

e 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 a orded 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. e gure of 19% is therefore probably an underestimate.

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

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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,

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involved, has a complex web of probable immune dysregulations and counter balances.

In England, those su ering 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 in ammatory processes, leading to a higher risk of becoming bed ridden and the consequent e ects thereof [17]. ere is now an abundance of evidence to show that those with neurological conditions experience higher levels of background in ammation [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 e ect of the January 2015 in uenza outbreak.

e potential involvement of the immune manipulating herpes virus, cytomegalovirus (CMV) has been suggested to occur in these events. e 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 RNA's within the viral capsule [34]. Very high

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 ag 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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