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Year-to-year Variation of Deaths in English Small Areas, and the Interaction Between a Presumed Infectious Agent and Influenza in 2015

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Abstract

Deaths in England and Wales in 2015 showed the largest increase over the previous year seen in nearly 50 years. This was partly due to a seasonal influenza outbreak in late 2014 with deaths peaking in January 2015, however, deaths had already shown a step-like increase earlier in 2014 due to an outbreak of a presumed infectious agent. Outbreaks of the other agent between 2002 and 2014 were characterised in very small areas, and this was compared to behaviour in 2015. Both agents were shown to have the potential to spread across all parts of England and Wales. Latest research in immunology is employed to demonstrate that the unusually high deaths in 2015 could have arisen from sequential infection within an overarching framework of the infectious burden in humans. The interaction between the other agent and influenza illustrates how a chance series of events, which may include influenza vaccination, can generate

unexpected large increases in mortality and morbidity.

Keywords: Emering infectious diseases, all-cause mortality, immune impairment, cytomegalovirus, influenza vaccination, medical admissions, gender.

Introduction

The spread of infectious agents is best detected using small area data. The population of the UK is clustered into a nested series of spatial hierarchies. The smallest spatial unit is an Output Area (OA) which contains an average of 309 persons in England and Wales. All census data is collected at OA level, and based on the 2011 census data all OA have been allocated to one of 72 social groups called the Output Area Classification (OAC). OA are then aggregated to Lower Super Output Areas (LSOA), which are then aggregated to Mid Super Output Areas (MSOA), and then to Local Authority (LA). In 2011, there were 181,408 OA in England and Wales containing an average of 129 households and 309 persons; 34,753 LSOA (672 households. 1614 persons); and 7,201 MSOA (3,245 households, 7,787 persons) [1]. Vital statistics such as population, births and deaths are all aggregated at OA level.

Evidence for a recurring series of presumed infectious outbreaks of a novel agent affecting both medical admissions and deaths has been recently published in SMU Medical Journal [2,3]. These surges in admissions and deaths show spatial spread along with age and condition dependence [4-23]. These features are highly suggestive of a new type of infectious outbreak which may have a *modus operandi* based on immune manipulation, leading to changes in susceptibility to infection, inflammation and autoimmunity [24-27]. These outbreaks also appear to be driving the unexplained increase in medical admissions, bed occupancy, and costs seen in the UK and elsewhere [28-32], and are so large that they even interfere with the calculation of hospital standardised mortality rates (HSMR) [33]. The closest clinical match appears to be with the ubiquitous immune modifying virus Cytomegalovirus (CMV), which can act via both clinical and sub-clinical routes upon human health [5,8,13,20,24-28].

Between 1950 and 1990 national examples of these outbreaks occurred roughly twice per decade, however, from 1993 there was a seeming shift to every three years, and since 2000 a shift to every two years [4,7-12,15-23,26,29]. The level of synchrony between small areas has been especially high in the 2012, 2014 and 2016 outbreaks, while that in the 2010 outbreak was low making it difficult to discern that a national outbreak had occurred [7,18,22-24,26-28]. These events appear to evade traditional mortality-based disease surveillance due to a novel type of relatively slow small area (or small social network) spread, which leads to the effects in one small area cancelling out the effects in another [34,35].

The unique feature of these events is that after initiation, the deaths, medical admissions, NHS sickness absence and the gender ratio at birth in each area remain high for approximately 12 months before suddenly reverting to the usual baseline, with deaths showing a 1 to 2-month lag after medical admissions, i.e. initial illness precedes eventual death [4,6-29,36,37]. Further unpublished analysis shows that a similar previously reported step-like change in the gender ratio [36], seemingly occurring in the first trimester, appears to precede the rise in medical admissions by around one month. The step-like increase in sickness absence among NHS staff is far higher than that observed in non-NHS public servants, suggesting that health care workers experience higher occupational exposure (unpublished analysis).

This on/off or high/low behaviour in deaths and medical admissions is the source of considerable ‘shock’ capacity and cost pressures in both health and social care, since the bulk of a person’s lifetime acute hospital care occurs in the last year of life [10,13,26,38].

An outbreak which occurred across 2012 and 2013 led to a minimum of 45,000 excess deaths in England and Wales [10,27], while another in 2014 led to even higher levels of apparent deaths due to unusually high synchrony in the spread of the agent [19,28,29]. The 2014 outbreak also appeared to interact with a seasonal influenza outbreak occurring in late 2014. This

interaction led to a prolonged period of higher deaths not observed for both agents acting alone [37].

Previous studies have investigated the effects of outbreaks of this agent upon medical admissions and deaths at national, local authority, hospital, GP practice, MSOA and LSOA level [2,3,7,9-12,15-18,21-27,30], and this study seeks to investigate the effect on deaths at the smallest possible level via OAs, within the context of a supporting social group classification for those OAs. This study will investigate the effect of these presumed infectious events on the time trend of annual deaths in English and Welsh Output Areas (OA) between 2001 and 2014, and will further investigate a potential interaction between the 2014 event with the late 2014 influenza outbreak, and the spike in deaths in early 2015[37]. The geographic distribution of instances of very high increases in deaths for both agents will also be investigated.

Materials and Methods

Monthly deaths in England and Wales were obtained from the Office for National Statistics, and those for Scotland from National Records of Scotland.

Annual deaths (all-cause mortality) for males and females in each of 181,408 OA within England and Wales between 2001 and 2015 were obtained by request from the Office for National Statistics. The geographic location (population centroid) of each OA in meters north and east of the UK reference point (off the coast of Cornwall) was obtained from the Office for National Statistics, as was the Output Area social classification (OAC) for each OA.

The magnitude of the difference between one year and the next was calculated as a standard deviation equivalent (STDEV) using Poisson statistics or as a percentage difference, both relative to the 13-year average for the number of deaths in each OA. STDEV = (year 2 – year 1)/square root (average deaths) or Percentage difference = (year 2 – year 1)/average deaths. The combined effect of influenza plus the other agent was investigated by a paired comparison

between 2015 and 2014.

Based on previous studies any change between paired years of less than + 2 STDEV was considered too small to evaluate whether the increase was due to chance or the action of an infectious outbreak.

The average of the maximum step-increase in deaths for each social group was calculated after excluding those OA which failed to achieve a +2 STDEV equivalent increase. Upper and lower 95% confidence intervals were calculated using the standard error of the mean.

Results and Discussions

Background

Up to the present, the trends in all-cause mortality have been assumed to reflect a wide range of environmental (temperature, humidity, etc) and infectious events (mainly winter respiratory infections). Unexplained deviations have been assumed to be 'one of those things'. However, with the benefit of hindsight, it is now known that certain years are characterised by the spatial spread of a presumed new type of infectious condition [2-31].

Before investigating the trends, the strengths and limitations of the data and its interpretation need to be discussed. Firstly, this study is attempting to look for evidence of spatial spread of a potential novel infectious agent between very small spatial units. An OA contains an average of 300 persons which corresponds to around just 130 households. OAs contains an average/median of 1.4/1.07 male or female deaths with maximum, minimum, upper and lower quartile respectively (0.07 to 47.14, and 0.71 to 1.57). OAs cover every possible combination of deprivation, urban versus rural, and ethnicity seen in England and Wales. Due to issues of confidentiality, the ONS will not release data where individuals could be identified. An OA is a very small area, hence the data is only released on a calendar year basis, i.e. potential date of death cannot be inferred, as may be possible if monthly data were available. On the other hand,

annual data has the advantage that the inherent seasonality in deaths has been largely minimised, and a like-for-like comparison is possible [30]. The larger annual total will also contain less statistical scatter. Hence the approach used in this study is to look for changes which are beyond the limits of simple Poisson variation, which must have arisen from a systematic difference between the two years.

If the infectious agent can achieve initiation at any point in the year, and to then remain active for a further 12 months, it follows that a series of year-to-year comparisons may fail to identify an outbreak which occurs toward the middle of the year. However, this key limitation is addressed by having access to deaths for both males and females covering more than 181,000 OA over a 14-year period, i.e. covering seven potential outbreaks in each OA. Therefore, a large outbreak of the agent is likely to occur at least once, with initiation toward the start/end of a year in each OA. Also, the magnitude of events initiating closer to the end or start of a calendar year may be underestimated, therefore, calculated average magnitude can be considered to be conservative.

The standard deviation of a Poisson distribution is, by definition, equal to the square root of the average. This relationship allows the difference between each year, and the average to be expressed as standard deviation (STDEV) equivalents. This transformation adjusts the results from OA with different average number of deaths into a common unit of comparison.

Over the time of the study only 0.8% of OAs had no deaths. Most OA contain stable populations, however there was a national trend to lower absolute number of deaths over the earlier years of this study. This trend would only lead to underestimation of any step-increase between years. The use of the average number of deaths over the 14-year period is justified because it gives conservative estimates of the magnitude of any step-increase, i.e. the calculated average deaths includes any higher deaths in the earlier years, and also includes any outbreaks of the agent. All results are therefore conservative estimates of any step-increases. As a further

check, the magnitude of both step-up and step-down after cessation of the outbreaks were compared. Apart from a tendency to slight over-estimation of the step-down in the earlier years both estimates of maximum increase were consistent (data not shown). To maintain a conservative approach only step-up following initiation has been used in this study.

Mortality Trends in the UK

To illustrate the different types of infectious events investigated in this study, Figure 1 presents a running 12-month total of deaths in England, Scotland and Wales (2011 to 2016), relative to the point of minimum deaths for each country.

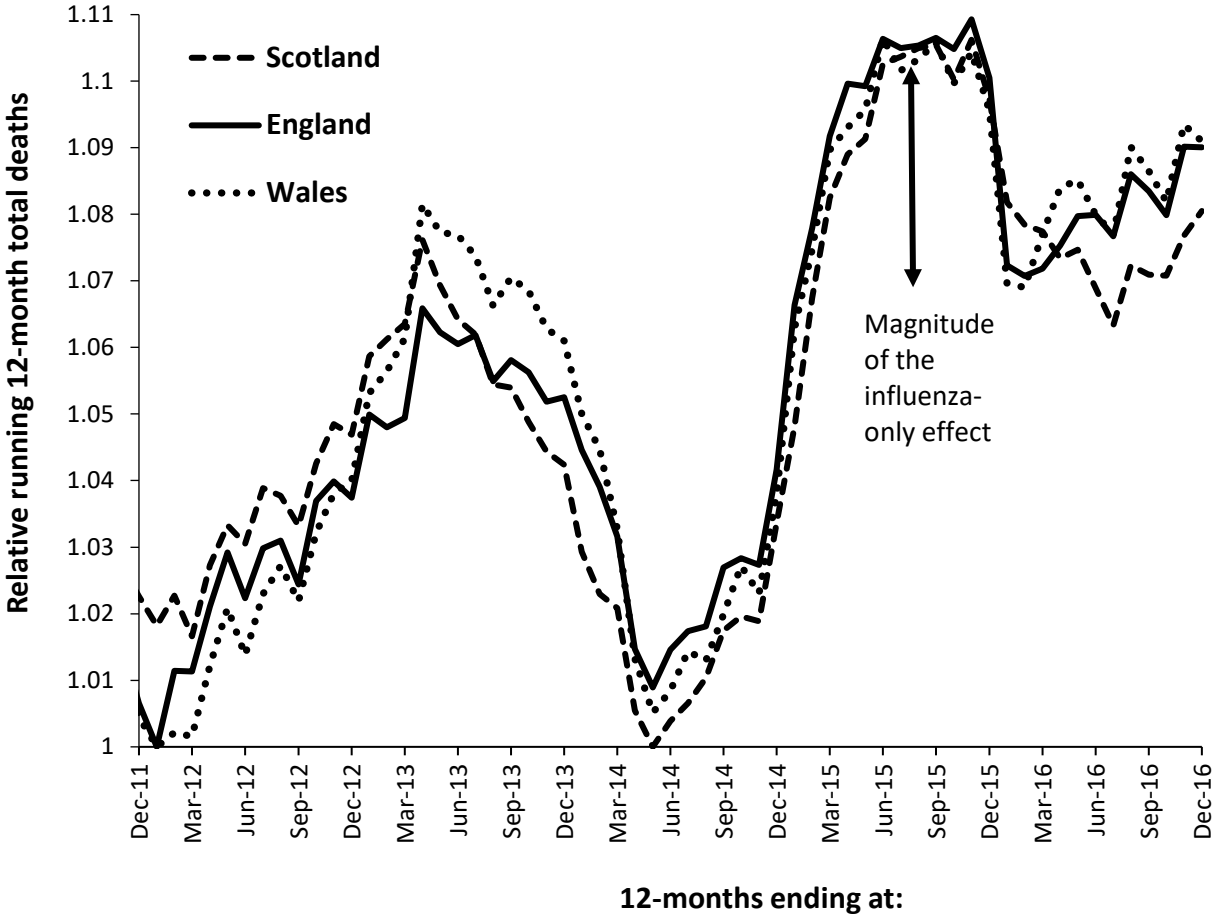

Figure 1. Running 12-month total deaths in the UK relative to the point of minimum 12-month total deaths.

Running 12-month total charts generate saw-tooth features for the start and end of step-like changes in deaths, while spike events such as influenza generate a table-top shaped feature. The first saw-tooth feature arises from an outbreak of the other agent commencing around January 2012. Deaths immediately jump up by around 6% to 8%, stay high for around 12 months, and then suddenly revert back to baseline around April 2013. See [23] for greater detail. The modest influenza event in the winter of 2014/15 generates a spike in deaths in January 2015 leading to the table top feature, however, another outbreak of the other agent had already commenced around June of 2014. In the absence of the influenza event a saw-tooth feature similar to that in 2012 would have occurred. By 2016 deaths should have reverted back to baseline, however, another outbreak of the other agent (earlier in England and Wales, later in Scotland) acts on top of an influenza-other interaction to keep deaths at a high level.

It must be emphasized that the health and social care systems in the three countries are run as separate entities, with different levels of funding, policies, public health strategies and management styles and structures. Hence commonality in Figure 1 is independent of structural and policy features. Likewise, the saw-tooth feature in Figure 1 has been documented over many years back to the 1950's [10], and occurs in all Western countries [21,26,30]. There is no demographic explanation for the behaviour [28,29,38].

With this background in mind we can now investigate the effects upon deaths observed at very small area.

Role of Gender

A disposition to slightly higher female deaths has been noted in previous studies [5,13,14,19,20,23,24,28]. It has also been noted that an outbreak of the unknown agent can initiate at variable times in the male and female population of an MSOA [23]. The disposition to higher female deaths is insufficient to warrant further investigation, however, the variable lag between the two genders for initiation implies that the male/female split should be retained, especially in this study, which only uses annual data, i.e. it is more likely to capture maximum amplitude outbreaks by analysing separate male/female data than using combined numbers of

deaths.

Small Area versus National Outbreaks

Throughout the text reference will be made to the dates of national outbreaks such as 2002, 2008, 2012, 2014 and 2016 (as per Figure 1), which apparently arise when the synchrony between small area outbreaks is far higher than usual. Apart from Figure 1 this study focusses on:

1. Maximum amplitude examples from each OA
2. The frequency of these outbreaks in each year
3. Spatial distribution of the other events up to 2014, and the influenza event in 2015
4. Potential interaction between the agent and influenza in 2015

Continuity with Previous Studies

This study extends previous analysis at country (international), local authority/county/province, MSOA and LSOA down to the smallest possible spatial unit. Maximum step-increase in deaths exceeding + 2 STDEV for male and female deaths are presented in Figure 2.

The results in Figure 2 are entirely compatible with all previous studies such that all fall along the same trend line with consistency between countries [23,30]. This study confirms that somewhere around a +1,000% increase in deaths is achievable in small social networks. The magnitude of the apparent increase decreases with size [30] due to complex spread between networks leading to outbreaks hiding themselves in their own (relatively slow) spread [35].

The apparent striations in Figure 2 arise from the fact that deaths are integer events. Hence the lowest striation represents a change in deaths equivalent to + 2 STDEV difference, and each striation above this has successively higher STDEV equivalent of difference.

Given the role of Poisson variation in small number events, data along the lowest

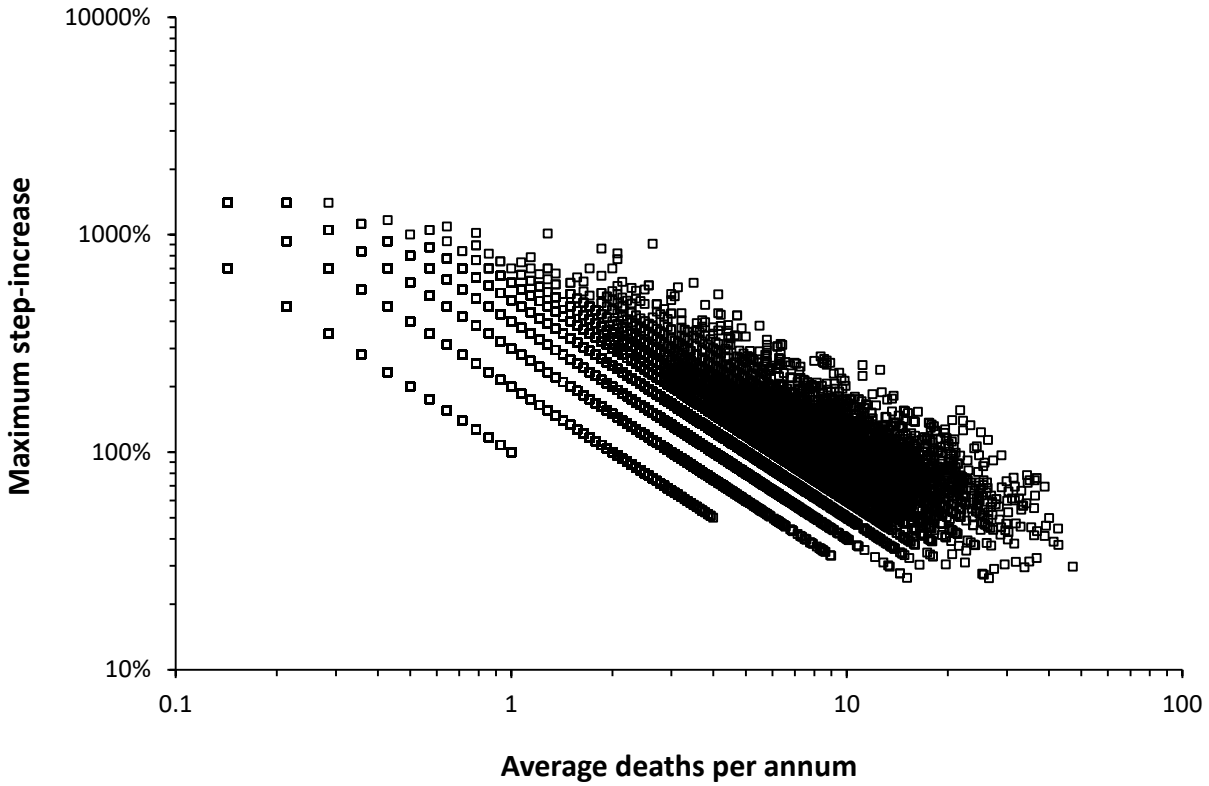

Figure 2. Maximum percentage step-increase in male and female deaths for OAs in England and Wales (2001 to 2014)

striation may be expected to have been diminished by Poisson randomness, while those along the top edge of the data may have been increased by randomness. The bulk of data toward the heavily populated middle will be largely free from chance-based uncertainty.

Frequency of Maximum Magnitude Outbreaks

A previous study at MSOA level using monthly data concluded that a maximum amplitude outbreak was commencing in around 0.9% of MSOA at any point in time [23], i.e. there is a low background level of outbreaks. Data from this study indicate that maximum amplitude outbreaks occur in between 12.8% (in year 2014) to 14% (in 2003) of OAs (data not shown). This is equivalent to a maximum outbreak initiating in 1% of months. Due to the possibility of underestimation arising from the use of annual numbers, these figures include

instances of the maximum increase occurring more than once, and OAs where the maximumincrease was less than +2 STDEV. Both studies therefore confirm that in each month a maximum amplitude outbreak is commencing in around 1% of OAs.

Maximum Magnitude of the Outbreaks

Table 1 summarizes the count of OA which contain an outbreak exceeding certain STDEV equivalents. The column '2001-2014' summarises the maximum event for the other agent in each OA over the 14-year period, while the column '2014' gives any OA exceeding these thresholds in 2014. The column '2015' gives a similar count for 2015, which includes the impact of the influenza outbreak in late 2014 on the spike in deaths in January 2015, and continued higher deaths arising from presumed interaction between the two agents [37].

Given that outbreaks of the other agent occur in all years it is possible that an outbreak of the other agent in 2014 could mask the effects of influenza in 2015. For example, an outbreak in 2014 could lead to a +4 STDEV increase in an OA, however, it would normally be expected that a corresponding –4 STDEV step-down would then ensue in the following year. A +6 STDEV increase due to influenza would then be partly masked by the -4 STDEV step-down, etc. To further avoid a -3 STDEV step-down cancelling out a subsequent +3, the maximum of 2015 or 2014+2015 was then determined for each OA. To account for this possibility the column '2014+2015' gives this maximum to reveal that a degree of masking did occur. As can be seen in Table 1 incidence of 2 to 6 STDEV examples of the influenza outbreak were underestimated by 40%, and of >6 STDEV by up to 55%.

This is further illustrated in Figure 3 where around 1,100 OAs experience greater than a +4 STDEV magnitude step-increase each year between 2002 and 2014 (years where influenza activity is low), while 2015 contains 4-times as many OAs experiencing such a large magnitude increase.

Table 1. Count of Output Areas exceeding certain standard deviation equivalent thresholds for outbreaks of the other agent (2001-2014), and for the combined influenza event in 2015.

STDEV	Other agent		Influenza +	
	2001-2014	2014	2015	2014+2015
2	225,351	25,552	31,409	43,981
3	78,123	6,625	10,695	15,024
4	14,893	1,259	3,081	4,365
5	2,822	290	1,137	1,622
6	398	56	408	562
7	74	20	230	313
8	16	6	85	132
9	4	3	65	97
10	2	1	52	80
11	2	1	42	61
12	1	0	28	38
13	1	0	20	31
14	1	0	18	28
15	0	0	15	21

Finally, Figure 4 shows the equivalent to Figure 1 except that the percentage increase in the 2015 event is displayed on the chart. As can be seen the percentage increase in deaths is higher than that seen in Figure 1, reflecting the combined effect of influenza plus the other agent in 2015. The combined effects of the two agents also leads to a higher proportion of greater than 1,000% increases in the interval 0.1 to 1 average deaths per annum. Also, the intercept of the underlying trend occurs above 1,000%.

While these are very high percentage increases, recall that only 12% of OA were affected by the 2015 event, which is slightly higher than the 7% to 8% of OA affected by the outbreaks of the other agent. Also, that maximum amplitude events probably only occur in each OA once every 10 years.

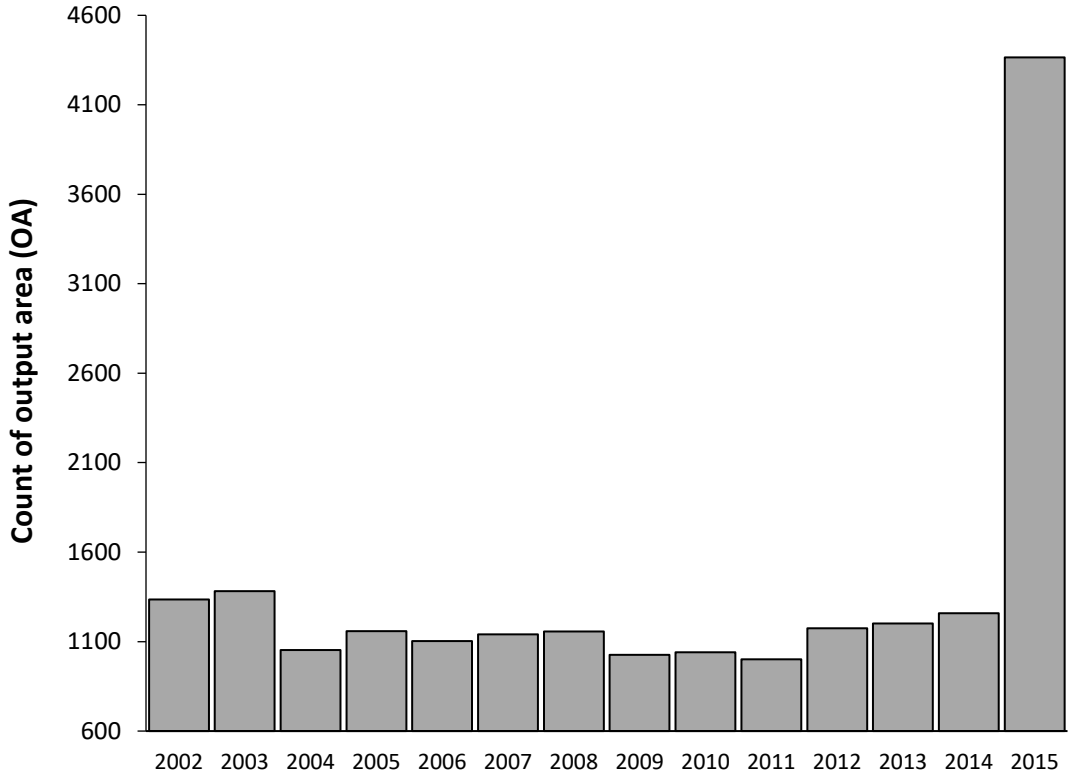

Figure 3. Count of OA experiencing greater than a +4 STDEV equivalent step-increase in deaths for various years (relative to the previous year)

Geographic Distribution

It is useful to compare the geographic distribution of the other agent and influenza plus the other agent in 2015. A random sample from both can be obtained by taking the top 1,000 OA with the highest STDEV increase from each group. For 2015, this resulted in selecting OAs with >5 STDEV male or female increase, and for 2001 to 2014 with OAs having >5.6 STDEV male or female increase. As can be seen from Figure 5 instances from both are clustered in the largest towns and cities due to higher population density, but with random occurrences elsewhere, i.e. both agents are ubiquitous with ample opportunity to sequentially co-infect individuals.

Analysis of maximum increase by distance north reveals that there is no apparent north-south gradient over the 567-kilometre (km) differential between south and north of England (data

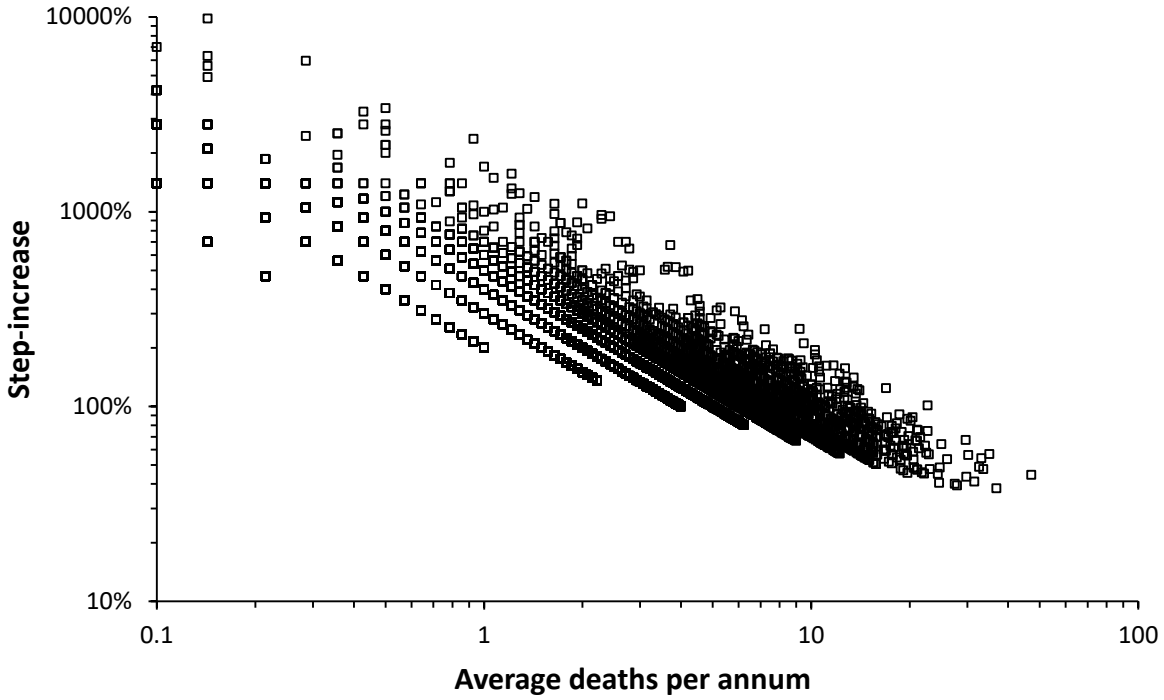

Figure 4. Percentage increase in male and female deaths in 2015 in OA (>2 STDEV increase)

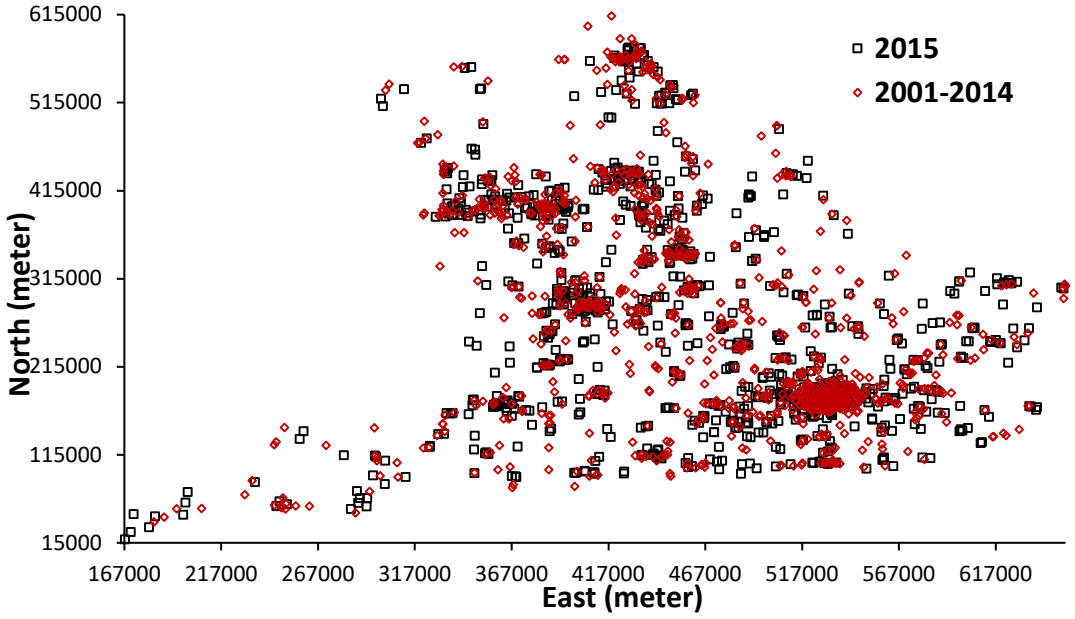

Figure 5. Geographic distribution of the top 1,000 OA with a very high increase in deaths for the 2015 event and the presumed infectious outbreak in previous years

not shown). Absence of a North-South gradient for these outbreaks has also been demonstrated in Australia [22].

The outbreaks of the other agent are also highly localised. For example, in 2004 four output areas in Liverpool all within 1 km of each other showed the following male/female changes in STDEV equivalents, E00176744 (+2.9/-2.5), E00176767 (-0.8/+1.7), E00176762 (+1.1/0.0), E00176759 (0.0/0.0). This is entirely consistent with highly granular infectious outbreaks moving via random contacts in social networks.

Role of Social Group

The OA classification (OAC) of social groups takes census variables such as rural/urban, housing type, unemployment, types of employment, age profile, ethnicity, and allocates each OA to one of 72 social groups [1]. These groups can then be used to investigate the relative contribution of random passage of the respective infectious agents along social networks versus susceptibility to infection due to social factors such as age or ethnicity.

Figures 6a, 6b and 6c give an overview, where the range between highest and lowest social group is generally around 0.4 STDEV. Note that only every second social group is displayed on the X-axis. As expected the 2015 event has the highest overall average, while the two single year measures have the widest 95% confidence intervals due to smaller numbers (especially in certain of the smaller national social groups). In all cases the two tails contain groups where the confidence intervals do not overlap, i.e. the OAC of social groups has achieved a measure of discrimination within the wider population. However, it is not known which elements within the OAC were responsible for this discrimination. In general, social groups containing high numbers of students tend to be in either tail.

Several social groups displayed a statistically significant difference between the magnitude of the outbreaks of the other agent and the combined event in 2015 and these are

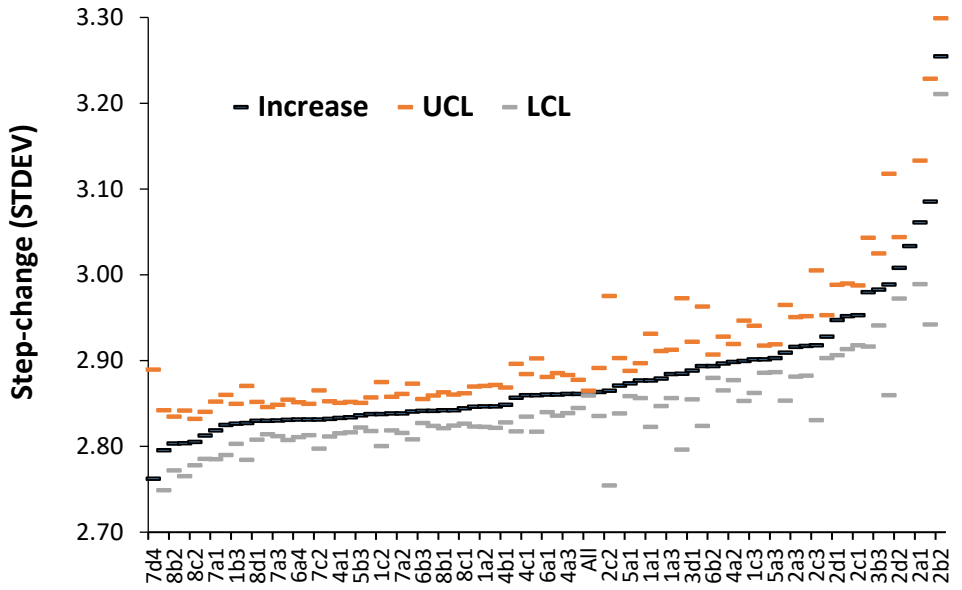

Figure 6a. Increase by social group for the events prior to 2015

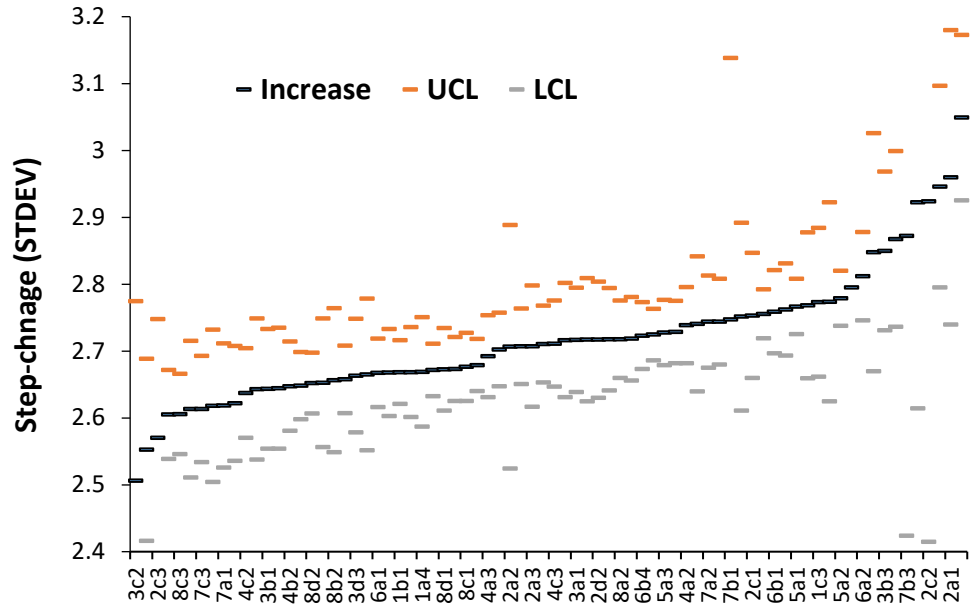

Figure 6b. Increase by social group for the 2014 event

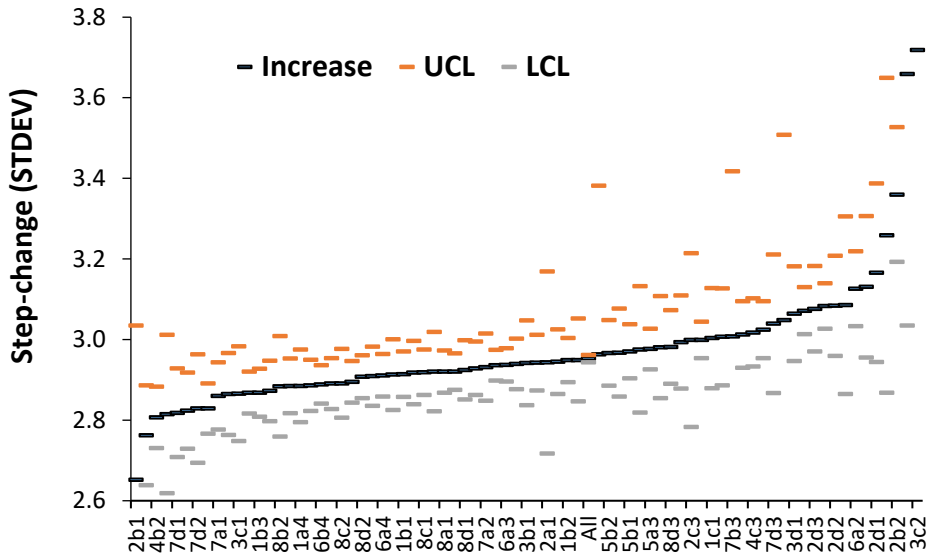

Figure 6c. Increase for the 2015 event by social group

given in Table 2 where it can be seen that the increase for the 2015 event was typically 2.5% to 7.5% higher than for the other agent alone. Recall that the calculated average for the other agent is the maximum response in each OA over the period 2001 to 2014, while that in 2015 is only for a single year.

In conclusion, segmentation of the population using the OAC generates moderate gradients between social groups which are statistically significant in the two tails and statistically significant between the other agent and the combined 2015 event. Further work is required to determine if something like age-standardization may yield better discrimination.

When does Influenza Interact with the Other Agent?

The increase in deaths in 2015 compared to 2014 was the largest single year increase since 1967 to 1968 [39]. There was a large increase in January 2015, higher deaths for the next three months and a tail of slightly higher deaths for the rest of the year. Influenza was partly implicated and deaths among those with Alzheimer's and dementia were especially high [39].

Table 2. Social groups where the 95% confidence intervals did not overlap between the magnitude of the maximum increase of the other agent (2001-2014) and the 2015 combined event, gap between CI increases from top to bottom of the table

OAC	Super Group	Group	Sub-Group	2001-2014		2015		Difference
				Increase	95% CI	Increase	95% CI	
8d1	Hard-Pressed Living	Migration and Churn	Young Hard-Pressed Families	2.83	0.02	2.92	0.07	3.4%
8c1	Hard-Pressed Living	Hard-Pressed Ageing Workers	Ageing Industrious Workers	2.84	0.02	2.92	0.06	2.6%
8b1	Hard-Pressed Living	Challenged Terraced Workers	Deprived Blue-Collar Terraces	2.84	0.02	2.95	0.08	3.6%
1c2	Rural Residents	Ageing Rural Dwellers	Renting Rural Retirement	2.84	0.04	2.99	0.11	5.5%
1b1	Rural Residents	Rural Tenants	Rural Life	2.83	0.02	2.91	0.06	2.8%
6a4	Suburbanites	Suburban Achievers	Ageing in Suburbia	2.83	0.02	2.91	0.05	2.8%
5a3	Urbanites	Urban Professionals	Families in Terraces and Flats	2.90	0.02	2.98	0.05	2.5%
4b1	Multicultural Metropolitans	Challenged Asian Terraces	Asian Terraces and Flats	2.85	0.02	2.94	0.06	3.2%
6b1	Suburbanites	Semi-Detached Suburbia	Multi-Ethnic Suburbia	2.83	0.02	2.93	0.07	3.4%
4a2	Multicultural Metropolitans	Rented Family Living	Private Renting New Arrivals	2.90	0.02	3.01	0.08	4.0%
2d3	Cosmopolitans	Aspiring and Affluent	EU White-Collar Workers	2.92	0.03	3.08	0.11	5.5%
8d3	Hard-Pressed Living	Migration and Churn	Hard-Pressed European Settlers	2.85	0.03	2.98	0.09	4.7%
5b3	Urbanites	Ageing Urban Living	Self-Sufficient Retirement	2.84	0.01	2.92	0.05	3.0%
3d1	Ethnicity Central	Aspirational Techies	New EU Tech Workers	2.89	0.03	3.06	0.12	6.1%
1b2	Rural Residents	Rural Tenants	Rural White-Collar Workers	2.84	0.02	2.95	0.05	3.8%
6b3	Suburbanites	Semi-Detached Suburbia	Semi-Detached Ageing	2.84	0.01	2.94	0.04	3.4%
5b1	Urbanites	Ageing Urban Living	Delayed Retirement	2.84	0.02	2.97	0.07	4.7%
6b2	Suburbanites	Semi-Detached Suburbia	White Suburban Communities	2.89	0.01	3.00	0.05	3.6%
4c3	Multicultural Metropolitans	Asian Traits	Inner City Ethnic Mix	2.86	0.02	3.02	0.08	5.5%
6a3	Suburbanites	Suburban Achievers	Detached Retirement Living	2.83	0.02	2.94	0.04	3.8%
2c2	Cosmopolitans	Comfortable Cosmopolitans	Migrant Commuters	2.86	0.11	3.66	0.62	27.7%
6a1	Suburbanites	Suburban Achievers	Indian Tech Achievers	2.86	0.02	3.02	0.07	5.7%
All	All	All	All	2.86	0.00	2.95	0.01	3.2%
6a2	Suburbanites	Suburban Achievers	Comfortable Suburbia	2.93	0.02	3.13	0.09	6.8%
5a2	Urbanites	Urban Professionals	Multi-Ethnic Professionals	2.90	0.02	3.07	0.06	5.9%
5a1	Urbanites	Urban Professionals	White Professionals	2.87	0.01	3.08	0.06	7.3%

Reanalysis of the trends in deaths over many years has revealed that the other agent and influenza infrequently appear to interact in a synergistic way [37], and such infrequent interaction is confirmed in Figure 2. During the period covered by this study there have only been two influenza events of any note, and these will now be discussed.

Recall that this study is focussed on deaths in England and Wales, where some 75% of all deaths occur above age 70, and 50% above age 80. Also, that deaths are the pinnacle of the morbidity pyramid.

The first major influenza event was the 2009 Swine Flu A(H1N1) pandemic. Since influenza virus A(H1N1) circulated continuously between 1918 and 1957, most people born before 1957 had been infected with a H1N1 subtype. Due to relatively good cross-immunity between the strains persons aged 52 to 91 therefore largely avoided the effects of the 2009 Swine flu pandemic, and effects were therefore greatest in those aged under 52 who were highly unlikely to die [40]. From Figure 2 there was no apparent interaction between the Swine flu (H1N1) strain of 2009 and the other agent, and if any interaction did occur the effects were masked by the very low risk of such younger persons dying.

The seasonal influenza outbreak in late 2014 is far more complex than the Swine flu pandemic of 2009. During 2014, the dominant A(H3N2) and B strains of influenza underwent significant mutation after the antigen mix for the 2014/15 winter had been formulated by the World Health Organisation. The population of the northern hemisphere was therefore vaccinated with an inappropriate antigen mix during the final months of 2014. However, in late 2014 and early 2015 in England and Wales, rates of influenza-like-illness (ILI) and hospitalization for influenza were only slightly higher than usual [41]. For example, in Wales the peak GP consultation rate for ILI in the winter of 2014/15 was about the same as that in 2012/13, and only around 30% of that for the winter of 2010/11 [42].

Vaccine effectiveness (VE) for influenza in the USA (standardized across all ages) is usually

around 30% to 60%, however, can be lower as in 2004/05 (10%), 2005/06 (20%) and 19% in 2014/15 [43]. Vaccine effectiveness for General Practitioner (GP) consultations for confirmed influenza in the UK was reported to be only around 3.4% [44]. In Canada, vaccine effectiveness for A(H3N2) went negative to -16% (-13% for clade-3C.2a compared to +52% for clade-3c.3b) [45]. In Beijing, the 2014/15 influenza B vaccine effectiveness dropped to -31.5%, and overall VE declined from 70.6% for those aged under 5 years down to -66.7% in those aged over 60 years [46]. In Beijing, influenza A peaked in the last week of December while influenza B peaked in March [46]. Clearly both location, time and racial characteristics are also involved.

However, deaths showed an unexpectedly large increase during the second week of January in both England and Wales [41,42], especially in those with Alzheimer's and dementia [39,47]. Rather than the usual rapid decline in deaths following the seasonal influenza outbreak, deaths remained stubbornly high throughout the rest of 2015 [39,47], and the expected step-down following the 2014 outbreak of the other agent did not occur – as in Figure 1.

Examples of this highly unusual interaction between influenza and the other agent have been shown to have occurred following the winters of 1967/68, 1990/91, 1998/99, and may be characterised by a larger increase in female deaths than would normally occur in an influenza only event. Female deaths were higher in all age bands above age 45 for the 2014/15 event [37], and deaths were especially high in those aged over 85 [37], i.e. those born after 1930 and therefore having natural exposure to influenza A(H1N1) [40].

Given that the ubiquitous immune modifying virus cytomegalovirus (CMV) has been proposed as a likely candidate for the other agent, see reviews [5,6,8,13,24,25,27] where ability to increase all-cause mortality is highlighted, it is relevant to understand how CMV may modify influenza vaccination and immunity.

CMV and Influenza

The ability of CMV to interfere with influenza vaccine effectiveness and immunity is seemingly less appreciated within the influenza vaccination community than by CMV researchers [48]. Vaccine effectiveness relies partly on antibody production (measured using hemagglutination inhibition), and, also upon cytokine production. Cytokine production can be even more important than antigen production. For example, the World War I 'Spanish flu' epidemic is now known to have been so lethal in the young because it was able to provoke a cytokine storm [49], which acts via innate sphingosine-1-phosphate-1 receptor signalling [50].

CMV seropositivity decreases B cell responses to influenza vaccination in both the young and elderly [51,52]. Latent infection with CMV is associated with poor memory CD4 T-cell responses to influenza A core proteins in the elderly [53]. CMV seropositivity is also associated with disturbed adaptive immunity via lower NK cell INF-α, production, higher CD57/NKG2C expression and lower expression of IL-18Rα on NK cells [54]. Non-responders to influenza vaccination were characterised by high levels of anti-CMV IgG and higher percentages of CD57+CD28- lymphocytes, increased levels of TBF-αand IL-10, and decreased levels of cortisol [55]. Following vaccination enhanced Il-2 dependent NK cell IFN-γ responses were detected in CMV seronegative individuals [56].

Interaction with other medical conditions and medications is an overlooked area, and peak antibody response after influenza vaccination rapidly diminished with age for persons taking beta-blockers and who were CMV seropositive [57]. Studies among elderly with and without Type-2 diabetes (T2DM) showed that frailty was the single best measure of poor influenza vaccination response in either group. CMV seropositive was considered a driving force toward frailty which could be further enhanced by aspects of T2DM [58]. In this respect, certain statins have a potential effect via inhibition of CMV replication [59]. Statin use was associated with reduced vaccine effectiveness against influenza A(H3N3) but not influenza A(H1N1)pdm09 or influenza B [60]. In another study over nine influenza seasons statin use was associated with

an 8% to 10% percentage point reduction in vaccine effectiveness against medical admission for acute respiratory illness [61]. Exposure to dioxin, a widely distributed environmental contaminant, can also modify immune responses and stimulate CMV [62].

Hence, CMV, other conditions, toxins and medications all have the ability to modify the immune response to influenza vaccination and infection. In this respect, it is of interest to note that the effect of CMV production of anti-influenza antibody production (as measured by hemagglutination inhibition) is an area with highly conflicting outcomes depending on age, year of the study and location [52,55-57,63-65]. These conflicting outcomes may be explained by some of the above factors, plus the fact that different studies have used different antigenic mix depending on the year of the study and year of the vaccine, and vaccination history [63]. In the US, influenza related hospitalization increases with poverty [66], as does the rate of CMV infection [67,68].

Having established that there is ample evidence for the ability of CMV to depress influenza immunity in the elderly, it is now relevant to discuss issues relating to sequential infection by pathogens and the pathogen burden.

Sequential Infection with Pathogens and the Infectious Burden

The immune response to both vaccination and infection is hugely influenced by past events. For example, in the 2014/15 season in Canada influenza overall VE was +53% for those not previously vaccinated, this fell to -32% if previously vaccinated in 2013/14, and -54% for serial vaccination since 2012/13 [45]. It has been noted that in laboratory reared mice sequential infection with pathogens is required to create the gene and altered vaccine responses observed in commercial ‘pet’ mice [69]. These subtle genetic changes overspill into the apparent efficacy during clinical trials where inter-individual variability in the natural course of infections had the greatest effect on trial outcome [70]. Patients with common variable immunodeficiency (CVID) and unclassified antibody deficiency all show highly variable response to influenza vaccination

via both antibody production and T cell cytokine response [71], presumably due to specific genetic mutations and their interaction with genetic priming from sequential pathogen exposure. The competence of antigen specific CD8 T-cells to CMV-pp65 or influenza virus (Flu-M1) among 23 healthy adults likewise varied significantly, with a stronger response from T-cells with longer telomeres [72], with age and infection history (including CMV) presumably playing a role in this variation between individuals.

Infants first exposed to influenza H3 subtypes are less susceptible to fatal H7N9, while older individuals exposed as infants to H1 or H2 subtypes are less susceptible to fatal H5N1 [73]. Single year differences in this infant imprinting versus current strains was also shown to be the most important factor explaining mortality [73]. Outbreaks of the other agent are also characterised by single-year-of-age profiles in both medical admissions and deaths [14], implying similar infant imprinting to the first strain encountered of the other agent.

Sequential infection can act to enhance the infection with the second agent [74]. During the 2009 influenza pandemic in tropical regions co-circulation with dengue viruses led to additional severe disease cases of dengue. This situation could also be replicated in a mouse model [75]. In chickens, previous infection with virulent strains of Newcastle disease acted to reduce pathogenic avian influenza replication, disease and mortality [76]. Sequential infection of hamsters with different types of phlebovirus led to varying degrees of cross-protection depending on the sequence of previous infections [77]

Coinfection with multiple pathogens has been referred to as the pathogen burden in which CMV is a common factor [5,13,24,25,27]. Indeed, coinfection with CMV and another pathogen (including other CMV strains) usually leads to more severe clinical outcomes [5,13,24,25,27]. Either one or both above mechanisms could account for the higher deaths observed in 2015.

Deaths Among Those with Alzheimer's and Dementia

During outbreaks of the other agent deaths among those with Alzheimer's and dementia are especially increased [6,20,47], and even more so during the early 2015 event [47]. CMV has been implicated in these findings [6,20,47]. Enhanced sensitivity among those with an existing disease burden is illustrated in the World War I 'Spanish flu' pandemic, where higher male mortality was probably due to the higher tuberculosis prevalence in males [78]. Based on an unusual change in the gender ratio at birth during the Spanish Flu pandemic it has also been proposed that the other agent and influenza may have synergistically interacted at that time [28].

Other Deleterious Immune Effects from Influenza Vaccination

From the above discussion, it is evident that influenza vaccination, which is the immune equivalent to infection with a pathogen, occurs in a sequence of infectious outbreaks. This sequence may differ between individuals and locations. Outbreaks of the presumed infectious agent add additional complexity to the immune landscape.

Mid-2015 influenza vaccination in Australia (winter in the Southern Hemisphere) lead to a doubling in the frequency of allergy-related adverse events following immunization (AEFI). This occurred across all vaccine brands, i.e. the effect was due to the specific antigen mix in this vaccine [80]. Outbreaks of the new suspected infectious agent also result in increases for allergy-related admissions [81].

The same vaccine was used in late 2015 in the Northern hemisphere for the winter of 2015/16. It is of interest to note that deaths in 2016 in the UK did not return to the usual expected baseline. Hence was this due to the interaction between influenza vaccination in late 2014 and the earlier outbreak of the proposed infectious agent, or indeed, was the previous interaction further amplified by vaccination in late 2015 with an antigen mix known to increase allergy-related events? While influenza vaccination may be generally 'safe' it is clearly not specifically always safe, and especially so to the very individuals most likely to be susceptible to outbreaks

of the new disease.

Conclusions

Evidence to suggest that something 'unusual' was happening has been around for many years, but lacked a conceptual framework for the correct explanation [2,24-29]. This study has extended the analysis of deaths in England to very small areas, and has documented behaviour in immediately adjacent small areas only possible from an infectious outbreak. Both the other agent and influenza have been demonstrated to have the potential to occur ubiquitously. A combination of influenza plus the other agent led to very high deaths a certain OAs. The original hypothesis regarding the spread of a novel agent remains valid, and urgent investigation is required by Public Health agencies around the world. Any agent capable of causing a 1,000% increase in deaths in a very small social network, howbeit only once every ten years, will have the uttermost and most profound medical and public health significance, as will its ability to intermittently potentiate the adverse effects of influenza and/or influenza vaccination.

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Authors Column

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