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Deaths in English Lower Super Output Areas (LSOA) show patterns of very large shifts indicative of a novel recurring infectious event

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Abstract

Deaths in the UK and other Western countries show 12 month periods of unexplained and consistently higher deaths. Excess cold/heat or winter infectious outbreaks cannot explain why deaths would remain high for 12 months, and then suddenly shift back to a 'normal'. This study looks at annual deaths (all-cause mortality) between 2001 and 2013 for males and females in over 32,000 English Lower Super Output Areas (LSOA). Some 40% of LSOA showed at least one instance of a year to year change exceeding +2.5 standard deviations equivalent difference (compared with only 0.7% due to chance). The magnitude of the maximum difference was highest in women. Particular years showed evidence of a widespread switch to higher deaths. In very small social networks the maximum step-like change in deaths exceeds a + 300% increase. An event of alarming magnitude is showing a recurring time series similar to a slow-moving

'novel' infectious outbreak.

Keywords: Emerging infectious outbreaks, all-cause mortality, immune impairment, cytomegalovirus, medical admissions, gender.

Introduction

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 [1]. These surges in admissions and deaths show spatial spread along with age and condition dependence [2-20]. 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 [21-24]. These outbreaks also appear to be driving the unexplained increase in medical admissions, bed occupancy, and costs seen in the UK and elsewhere [25-28], and are so large that they even interfere with the calculation of hospital standardised mortality rates (HSMR) [29].

Since 2000 (in the UK), these events have been occurring at roughly two yearly intervals, although in very small areas this interval may, on occasion, vary from 1 to 3 years [5,7,9,15,16,19,20]. These events appear to evade traditional mortality-based disease surveillance due to a novel type of relatively slow spread, which leads to the effects in one small area cancelling out the effects in another [30,31]. Hence the effect observed at national level can vary from seeming absence to a large increase dependant on the degree of spatial synchrony for each outbreak [26]. After initiation, the deaths and medical admissions in each small area remain high for approximately 12 months before reverting back to the usual baseline, with deaths showing a 1 to 2 month lag behind medical admissions, i.e. initial illness precedes eventual death [24].

An outbreak which occurred across 2012 and 2013 led to a minimum of 45,000 deaths in England and Wales [8], while another in 2014 led to even higher levels of apparent deaths due to unusually high synchrony in the spread of the agent [13,26].

This short study will demonstrate the effect of these presumed infectious events on the time trend of annual deaths in English Lower Super Output Areas (LSOA) between 2001 and 2013, and will further investigate gender differences noted in the previous study [1]. In the UK, census data is collected at Output Area (OA) level, and this is then aggregated to larger geographies. A LSOA is a small area containing approximately five OA's and 1,500 persons, and will normally contain roughly similar socio-economic groups.

Materials and Methods

Annual deaths (all-cause mortality) for males and females in each of 32,000 LSOA within England between 2001 and 2013 were obtained from the Office for National Statistics website http://www.ons.gov.uk/ons/search/index.html?newquery=lsoa. 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 of number of deaths in each LSOA. STDEV = (year 2 – year 1)/square root (average deaths) or Percentage difference = (year 2 – year 1)/average deaths.

A count of LSOA exceeding ± 2 STDEV or ± 3 STDEV was determined in each year, and the maximum percentage difference between years was determined in all LSOA exceeding ± 2.5 STDEV difference between years, i.e. greater than the 99% confidence interval.

Results and Discussions

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 [5,7,9,15,16,19,20].

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. A LSOA contains an average of 1,500 persons (range 1,000 to 3,000) which corresponds to just 400 to 1,200 households. LSOAs contains an average of 7 to 8 deaths with maximum, upper quartile, median and mode for males (65, 9, 6, 5) and females (101, 10, 6, 4) respectively. LSOAs cover every possible combination of deprivation, urban versus rural, and ethnicity seen across parts of England and Wales. Due to issues of confidentiality, the ONS will not release data where individuals could be identified. A LSOA 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. 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 is able to 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 virtue of having access to data covering in excess of 32,000 LSOA over a 14 year period, i.e. covering seven potential outbreaks. 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 LSOA.

By definition, the standard deviation of a Poisson distribution is 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 LSOA with different average number of deaths into a common unit of comparison. Most

LSOA contain stable populations, and 65% of LSOA have less than a ± 3% trend (relative to the 13 year average) to higher or lower deaths over the 13 year time period, while on 99.6% of occasions the background trend is less than ± 0.5 STDEV equivalent. Given the high statistical thresholds used in this study, the effect on the worst affected LSOA showed that adjustment of deaths for any trend did not make a material effect on the calculation of differences between years. The use of the average number of deaths over the time period is therefore justified.

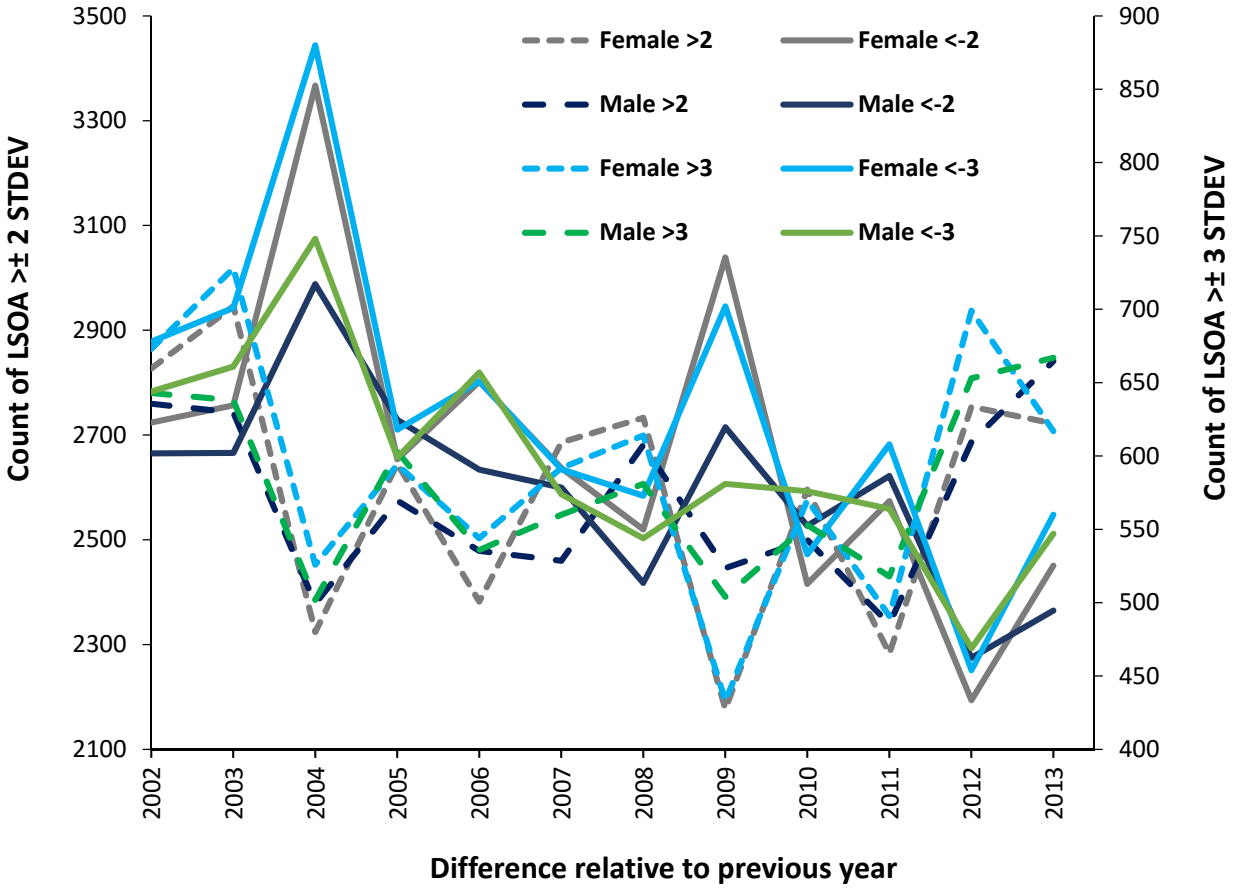
Two approaches are therefore employed. In the first, to conduct a count of year-to-year changes exceeding certain statistical thresholds, while in the second, to document the largest step-like change over the entire time period in each LSOA. The first method is designed to detect 'how often' while the second is designed to detect 'maximum potency'.

In this respect Figure 1 summarises the number of LSOA showing a change relative to the previous year which is beyond either a ± 2 or ± 3 standard deviation difference as defined by Poisson statistics. Compared to simple Poisson variation, the time series contains around 8-times more data lying beyond + 3 standard deviations (a statistically significant large step increase at initiation of an event), and 48-times more data lying beyond -3 standard deviations (a statistically significant large step-down following cessation of one of these events). As can be seen, large positive and negative differences simultaneously occur in the same year in different LSOA, although some years are marked by the predominance of a shift in one direction. Hence 2004 experienced a far higher number of large negative shifts (relative to 2003), while 2012 experienced more positive shifts (relative to 2011).

In searching for an explanation of these shifts, factors such as the weather, air quality, or any other metrological explanation can be immediately and categorically excluded, since large negative and positive shifts can occur in areas which are adjacent to each other. For example, in 2009 Adur 003A experienced a -2.0 STDEV equivalent shift while immediately adjacent Adur 003B experienced a + 2.9 STDEV equivalent shift. Numerous examples of this apparently confusing behaviour are available, with similar results replicated in other studies investigating

the simultaneous changes in medical admissions accompanying these events in different locations and at different times [5,7,9,15,16,19,20]. Indeed typical winter infectious agents can likewise be excluded since the extreme spatial granularity implied by these findings would not occur. Also note from Figure 1 that the magnitude of the step-like changes are always highest in females, and this is entirely consistent with the greater effect against female medical admissions which occur during these events [1,23].

Figure 1. Count of LSOA showing a large deviation in total deaths relative to the previous year



It has been proposed that the relatively slow spread of a novel type of infectious agent is

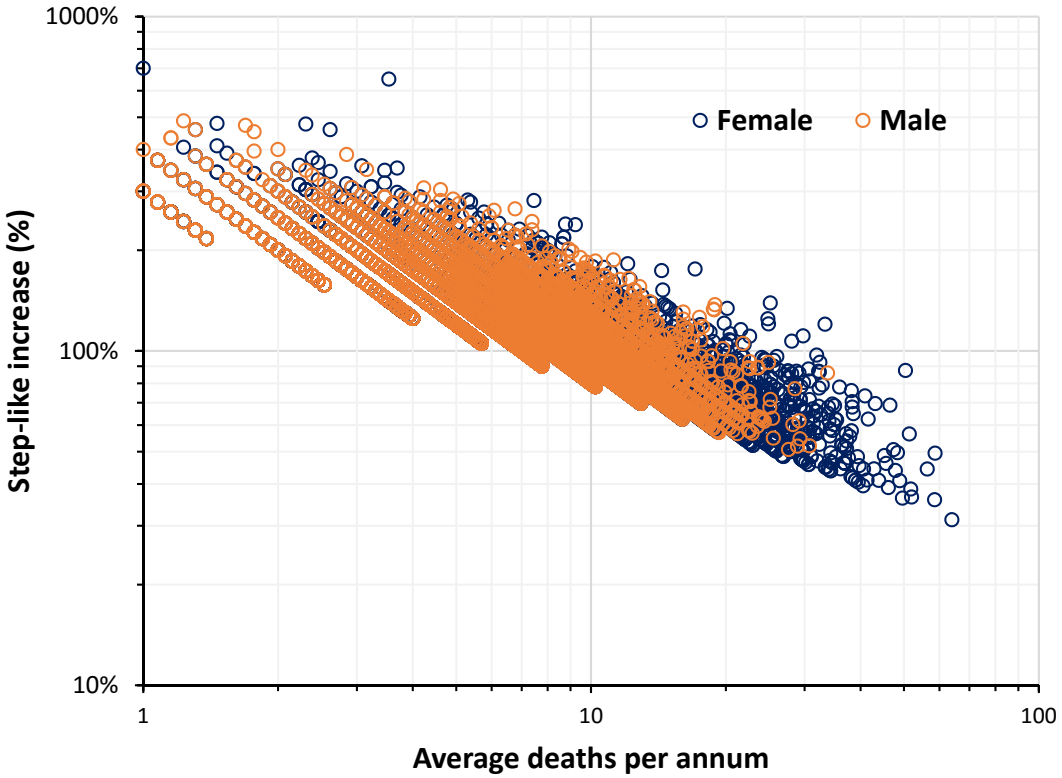
implicated [21-24]. Given that these unusual events appear to occur every two years, Figure 1 provides additional insight into how they have evaded detection via traditional disease surveillance methodologies. Due to the relatively slow spread between LSOA across England and Wales, there is a background level of statistically significant positive and negative shifts in every year which act to cancel each other out. Hence at national level 2005, (relative to 2004) and 2010 (relative to 2009), appears to show roughly no net difference.

Having demonstrated a profound effect upon all-cause mortality which occurs at a background level, and is also more evident in particular years, Figure 2 now investigates the maximum value of any resulting step-like difference between years for both males and females in each LSOA over the entire time period. While Figure 2 details the largest percentage difference, to give some idea of the profound statistical significance of these events, only step-like differences exceeding + 2.5 STDEV of difference (relative to the average) have been displayed. Some 40% of LSOA contain at least one example of such extreme deviation from one year to the next. Chance is categorically excluded, and very large systematic shifts are therefore evident. Note that in a Poisson distribution only 0.68% of the data lies beyond + 2.5 STDEV compared with 40% as in Figure 2. Also note that a +1.6 STDEV equivalent increase represents the 95% confidence interval normally applied to distinguish statistical significance, and that 85% of maximum values in MSOA fall above this threshold.

The apparent striations in the data in Figure 2 arise from the fact that deaths are integer events. Hence the lowest striation represents a change in deaths equivalent to + 2.5 STDEV difference, and each striation above this has successively higher and higher STDEV equivalent of difference.

A disposition to larger effects against females is evident. Male deaths do occur in LSOA containing greater than 20 deaths per annum, however, the magnitude of the step-like difference is insufficient to pass the ± 2.5 STDEV threshold required for data to be displayed in Figure 2.

Figure 2. Absolute value of the maximum difference in deaths between successive years in LSOA with greater than a + 2.5 standard deviation equivalent difference between years



Also note that the percentage difference in deaths increases as size reduces. On this occasion size is measured as the average number of deaths in each LSOA, and from an infectious transmission point of view could be considered to be proportional to the number of social networks in each LSOA. Simulation has demonstrated how the unique kinetics of these presumed infectious events leads to their apparent effect being diminished as the size of the spatial unit increases, i.e. there is greater opportunity for small area spread to cancel out the effects in another small area as the spatial/social network unit gets larger [9,20,26,31]. This leads to a sometimes imperceptible change at national level, which has hindered the earlier identification of these events.

Other studies have demonstrated that the LSOA exhibiting the highest step-like change will typically contain mostly persons of white British ethnic origin, will probably have one or more nursing homes, and will contain a higher proportion of elderly persons [7,9,20].

The final comment regarding Figure 2 is that the percentage increase in deaths observed in England is almost identical to those observed in Australia. The Australian study used Local Government Areas (LGAs) across the whole of Australia, which contained a number of small areas mostly in remote places where just one or two small communities would be present. This study also used data from an almost identical time series (2001 to 2012), however, opposite hemispheres imply that winter was not a common cause since it occurs in the middle of the calendar year in the southern hemisphere. In fact, all countries so far studied fall along the same trend line regarding the effects of size [26].

Some discussion is required around the apparent 12 month duration of these events. It would appear that onset of the apparent infection precipitates a time cascade of mainly inflammation based diseases/conditions, and exacerbation of existing conditions. Admissions showing a step-like increase at immediate onset appear to be due to unknown/unspecified viral illness, followed by opportunistic pneumonitis, progressing to more complex conditions [4-7,9-12,18,20-24]. Deaths show a similar time cascade of conditions [4-7,10]. My own unpublished analysis of inflammatory markers in critical care patients shows the same step-like increase at initiation. However, the effect on critical care admissions only endures for around 6 months. Hence, the apparent duration for 12 months is itself a complex composite picture derived from a time-based cascade of the consequences of the seeming immune disturbance initiated by this agent.

Lastly, a series of these infectious like events occurred during the 1990's, and it was noted that during the 1993 event there was a 37% increase in medical admissions for those in the age band 15 to 44 years [23]. A detailed actuarial study of deaths during this period showed that those aged 20 to 40 experienced a significant overall reduction in mortality improvement, i.e.

there was a cluster of earlier than expected deaths [32]. A recent study has likewise suggested that the age-standardised increase in medical admissions observed during these 'outbreaks' shows a peak in those aged 10 to 40 years [25]. The epidemiological evidence for a common theme is indeed emerging.

Conclusion

Evidence to suggest that something 'unusual' was happening has been around for many years, but lacked a conceptual framework for the correct explanation [1,21-24]. This study has extended the analysis of deaths in England to very small areas, and has documented apparently inexplicable behaviour in immediately adjacent small areas. 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 >300% increase in deaths in a small social network will have the uttermost and most profound medical and public health significance.

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