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Unexpected Single-year-of-age Changes in the Elderly Mortality Rate in England and Wales During 2012

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Author's contribution

This whole work was carried out by author RPJ.

Original Research Article

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ABSTRACT

Aims: To evaluate single-year-of-age specificity in deaths in England and Wales associated with a large, unexpected and unexplained increase in 2012. To demonstrate that this type of event has occurred previously across the entire UK. To demonstrate that infectious-like spread at a regional level in England may be involved.
Study Design: Longitudinal study of annual (calendar year) deaths (all-cause mortality) in the United Kingdom and England and Wales using publically available statistics available from the Office for National Statistics (ONS).
Place and Duration of Study: United Kingdom, England & Wales, local authorities within England & Wales covering a variety of time spans designed to illustrate various key points.
Methodology: Deaths between 1974 and 2012 in the United Kingdom. Live population and deaths for residents of England and Wales and of English local authorities. Calculation of single-year-of-age death rates in 2011 and 2012 which are the years before and after the large and unexpected increase in deaths.
Results: A recurring series of infectious-like events can be demonstrated which prior to 2000 had been largely assumed to be due to influenza epidemics. The event in 2012 shows specificity for the elderly particularly above age 75, which is somewhat expected given increased susceptibility to the environment as we age. The single year of age mortality rate shows saw tooth behavior for deaths in 2011 and even more exaggerated saw tooth behavior is seen in the difference between 2011 and 2012. Similar saw tooth behavior is seen in the difference between single-year-of-age standardized admissions

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via the emergency department in England between 2008 and 2012. The infectious spread across England behind this phenomenon is illustrated at regional level and probably results in a 40% underestimation of the saw tooth behavior.

Conclusion: The saw tooth behavior is known to be associated with what is called 'original antigenic sin'. Hence the saw tooth behavior appears to indicate that the unexpected high elderly mortality in 2012 was due to an outbreak of an infectious agent which has multiple strains. This behavior confirms the results of other studies investigating simultaneous increase in medical admissions to hospital during the time that the deaths increase. The ubiquitous herpes virus, cytomegalovirus may be involved, although at the moment this virus provides a prototype for the sort of immune modulating agent that may be responsible. The use of five year age bands to age standardize mortality and medical admission rates may be subject to misleading outcomes where the periodicity behind these outbreaks and their cumulative effect on immune mediated responses is out of synchrony with the basic saw tooth behavior seen in both mortality and admission rates. This has major implication to the calculation of hospital standardized mortality rates (HSMR).

Keywords: Mortality rate; excess deaths; infectious outbreak; emerging infectious diseases; cytomegalovirus; immune function; medical conditions; age; age standardization; HSMR.

1. INTRODUCTION

In England and Wales the absolute numbers of deaths have been declining from the mid-1990 due to ongoing improvements in life expectancy. Deaths are expected to reach a minimum by around 2015 to be followed by a gradual increase as the World War II baby boom begin to die in appreciable numbers [1]. In February of 2012 there was a totally unexpected, unexplained and sudden increase in deaths which continued through to mid-2013 when deaths reverted back to more usual levels [2]. This is not the first time that this unusual increase in deaths has occurred and previous occurrences in 1993, 1996, 2002 (main peak in 2003) and 2007 (main peak in 2008) have been documented along with simultaneous increases in emergency department attendances, medical admission to hospital, GP referrals and wider health care costs, all of which show infectious-like spatiotemporal spread and condition specificity [3-15]. More recently a curious cycle in the gender ratio at birth has also been shown to initiate with these events [16]. On all occasions deaths, especially among the elderly, had increased to the extent expected of a major influenza epidemic, however, influenza activity (in the winter) has been lower than historic levels since 2000 and before 2000 these presumed outbreaks appeared to potentiate the effect of winter mortality in the presence of influenza [1-2,10]. Are there hidden signatures in the mortality data which may shed light on this curious phenomena?

Up to the present mortality rates have been rarely calculated at single year of age increments and the default is to use 5 year age bands. This has usually been due to the fact that the denominator (the population of living people) is usually uncertain, especially as time progresses away from the 10-yearly cycle of population census. The recent 2011 census in the UK provides an opportunity to calculate single-year-of-age mortality rates by matching deaths in 2011 with the mid-year population and likewise for 2012.

The aim of this paper is to demonstrate that the bulk of unexpected deaths in 2012 were for the elderly and that curious single-year-of-age saw tooth movement in the mortality rate may offer a clue to the etiology of the source of the excess deaths.

2. METHODOLOGY

2.1 A Time Series of Deaths in the UK

Total deaths (1974 to 2012) for the entire UK by gender were obtained from the ONS. The background trend for males was calculated using a third order polynomial after excluding the spike years while for females a second order polynomial was applied after 1998, deaths being relatively constant prior to this point. Difference between actual and predicted was then calculated. Polynomial regression was performed using Microsoft Excel.

2.2 Age Profile for Excess Deaths in 2012

The age profile of the excess deaths for each gender in 2012 was determined by looking at the trend in deaths along year of birth cohorts, hence, deaths for those aged 90 in 2010 versus 91 in 2011, etc. This approach was necessitated by the impact of World War II on single year differences for particular elderly groups. Excess deaths in 2012 were then cumulatively summed by age and presented as a cumulative plot relative to the maximum extra deaths.

2.3 Single-year-of-age Standardized Death Rates

Single-year-of-age deaths in 2011 and 2012 for England and Wales and the 2011 census-based population in England and Wales was obtained from the ONS. Deaths were converted into a mortality rate per 1000 live persons. Single year of age population in 2012 was determined by incrementing the 2011 population forward by one year for each year of age and subtracting deaths in 2011 to derive the equivalent single year of age 2012 mid-year live population.

2.4 Single-year-of-age Differences in Admission via the Emergency Department

Single-year-of-age standardized admissions via the emergency department in 2008/09 and 2012/13 in England was obtained from the Health and Social Care Information Centre http://www.hscic.gov.uk/catalogue/PUB13040. The 99% confidence interval was calculated using Poisson statistics. Admissions per 1000 head via the emergency department in England during 2012/13 was obtained from the same source.

2.5 A Time Cascade of Deaths across England Originating in 2012

To demonstrate the impact of infectious spread throughout England each local authority (LA) was ranked from lowest increase in deaths in 2012 for those aged 80+ through to highest. Hence rank 1=East Cambridge shire with a 17% reduction (-17%) through to rank 327=Isles of Scilly with a +50% increase. This ranked data was then placed into larger government regions and the profile of the ranked data displayed for each region.

3. RESULTS AND DISCUSSION

3.1 A Time Series of Deaths in the UK

Due to improvements in life expectancy the absolute number of deaths in the UK has been declining for some time. The underlying trend in deaths in the UK since 1974 is roughly flat for females up to 1998 followed by a decline and for males shows a continuous decline since 1974. Both of these trajectories are interrupted by a series of large spikes, which prior to 2000 were associated with influenza epidemics. In early 2000 influenza activity dropped to a 100 year minimum, however, the large spikes continued to occur. Removing these spikes allows the calculation of a baseline trend (in the absence of large epidemic events) which can be subtracted from the actual deaths to accentuate the epidemic events.

This analysis is presented in Fig. 1 along with a series of arrows denoting the points where emergency medical admissions and other health care contacts exhibit an unusual step-like change in their trajectory [1-16]. As can be seen the large spikes in death continued beyond 2000 and cannot therefore be explained by influenza epidemics. The period of unusually low influenza activity was eventually interrupted by the late-2009 'swine flu' epidemic which peaked in early 2010 and this explains the small peak in deaths in 2010. The extra and unexpected mortality in 2012 amounted to around 15,000 female and 9,000 male deaths although as Fig. 1 demonstrates there can be a shoulder each side of the main peak.

Two recent studies have shed light on the nature of these shoulders. Firstly, a study of a monthly time-series of deaths in each of the area health boards (AHB's) in Scotland from 1990 to 2012 has demonstrated a series of peaks in deaths as per the arrows in Fig. 1, however, the increase in deaths shows curious spatial spread between AHB's which is highly suggestive of an outbreak of a relatively difficult to transmit infectious agent [11]. Even more curiously this infectious-like spread always commences earlier in Scotland than in England and this explains the earlier part of the shoulder surrounding each peak. The 2012 event seen in England & Wales commences in 2011 in Scotland which gives the 2011 shoulder in Fig. 1. Followed by movement into England and Wales in 2012 giving the large peak, and as will be discussed later there is a potential shoulder in 2013 from further spread within England & Wales.

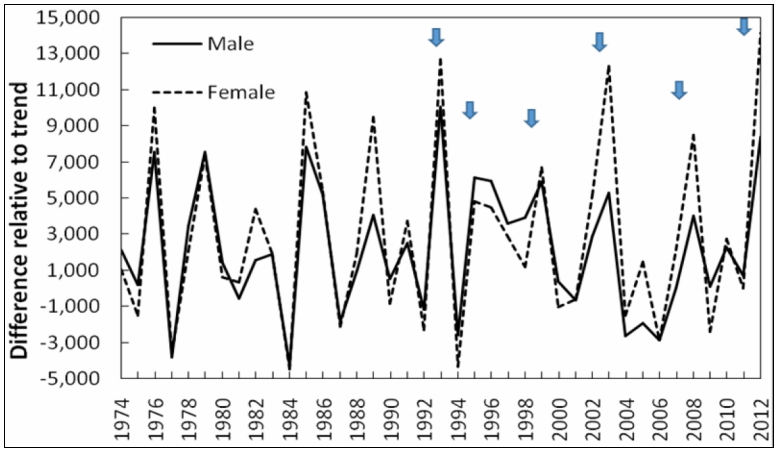

Fig. 1. Deaths relative to trend in the United Kingdom by gender, 1974 to 2012

A second study which focused on the 2003 and 2008 peaks across the entire UK also demonstrated evidence for regional spread across the entire UK over a three year period centered on the main peak, hence the shoulder after the main peak [15]. This study identified that the increased deaths were specific to certain conditions associated with hospitalization prior to death and the spread of an infectious agent seemed highly likely. The proposal of an infectious etiology is further strengthened by the observation that the gender ratio at birth also undergoes a characteristic temporary shift toward males at the points marked by the arrows in Fig. 1 [16]. Clearly the above suggests that we need to know greater detail regarding the specific details relating to death.

Due to the slightly earlier start of this infectious-like event in Scotland the following analysis will concentrate on deaths in England and Wales and conclude with analysis specific to England.

3.2 Age Profile for Excess Deaths in 2012

Age specificity can reveal hidden infections signatures and to illustrate this issue the cumulative age profile for male deaths in 2011 in England & Wales and the cumulative unexpected (additional) male deaths in 2012 is presented in Fig. 2. It can be seen that the extra deaths were concentrated in the age range 60 to 97 or 70 to 97 for females (data not shown). Note that the slight negative cumulative trend for males in Fig. 2 is due to significantly fewer than expected deaths for some ages between 35 and 60 which could be consistent with the proposed preference for this agent against females, an effect which also seems to apply to pregnancy [16]. While this information is useful it requires age standardization to account for differences in the age profile for both males and females. However the irregular nature of the cumulative charts seem to point to underlying single-year-of-age issues. Hence we have a potential disease or condition affecting mainly the elderly and with the potential for single-year-of-age effects and with some degree of gender specificity.

3.3 Single-year-of-age Standardized Death Rates

Fig. 3 presents the same data but shows the mortality rate in 2011 (England and Wales) for both males and females. The year 2011 is both the census reference year and the year before the unexpected increase. As can be seen the trend for both genders from age 19 upward is characterized by close to a logarithmic increase in mortality rate with age and also by a small degree of saw tooth behavior which is evident as the small wobbles in the trend lines. Note that the wobbles appear to diminish with age but this is due to the logarithmic scale.

The difference between the mortality rates in 2011 and 2012 are then compared in Fig. 4 where the saw tooth behavior becomes far more prominent.

This begs the question as to how the saw tooth behavior originates. A seminal paper published by Thomas Francis in 1960 introduced the concept of ‘antigenic original sin’ to explain the saw tooth relationship with age observed during influenza epidemics which originate from previous exposure to different strains of the influenza virus [17]. In original antigenic sin the immune system is primed by the exposure to the first strain which may or may not confer advantage upon next exposure to a different strain. The saw tooth effect arises from the time between these recurring antigen exposures throughout a person’s

lifetime. The 2008 peak in deaths along with its associated age specificity (unpublished) leads to the residual saw tooth behavior seen in Fig. 3 and in like manner the 2012 event will generate additional patterns which will be carried forward into future years.

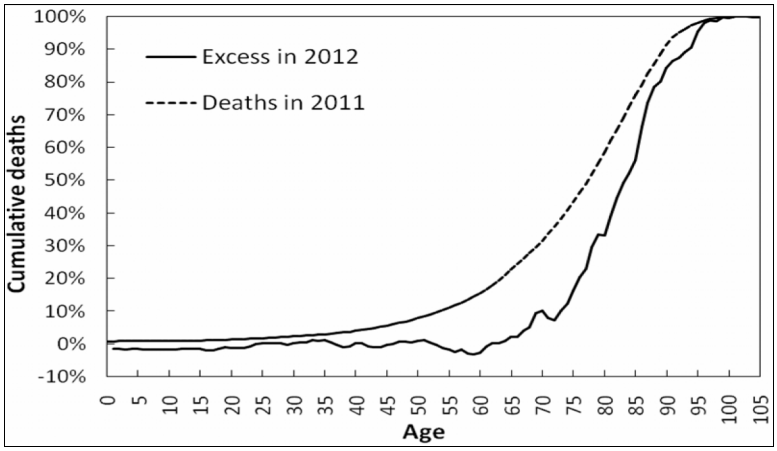

Fig. 2. Cumulative excess deaths for males in 2012 by age

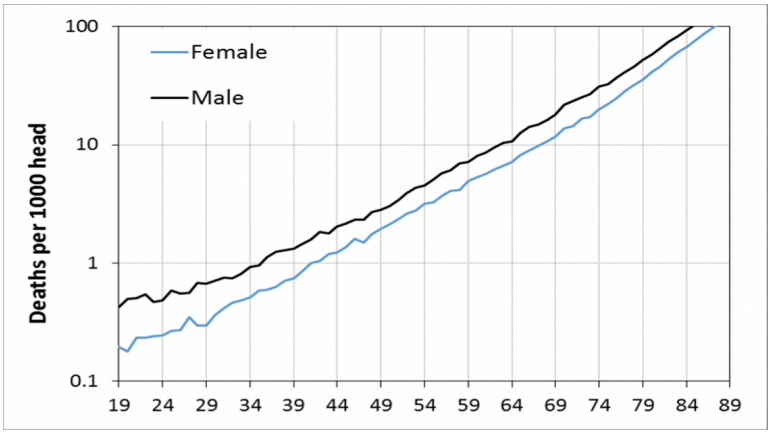

Fig. 3. Single year of age trend in mortality rate in England and Wales, 2011

However, due to the relatively small number of deaths for each age (a maximum of around 8,500 for males age 85 and 11,000 for females aged 89) the difference in the mortality rate is subject to fairly large 99% confidence intervals and we need to seek an alternative method to demonstrate that the saw tooth pattern is real. Such single-year-of-age saw tooth behavior has also been documented to occur in the increased medical admissions which accompany these events [6]. On this occasion an alternative source of single-year-of-age standardized data is available in the form of admission to hospital via the emergency department (ED). Due to the far larger numbers of admissions the 99% CI becomes more manageable. The next section will use such larger numbers to confirm the saw tooth behavior.

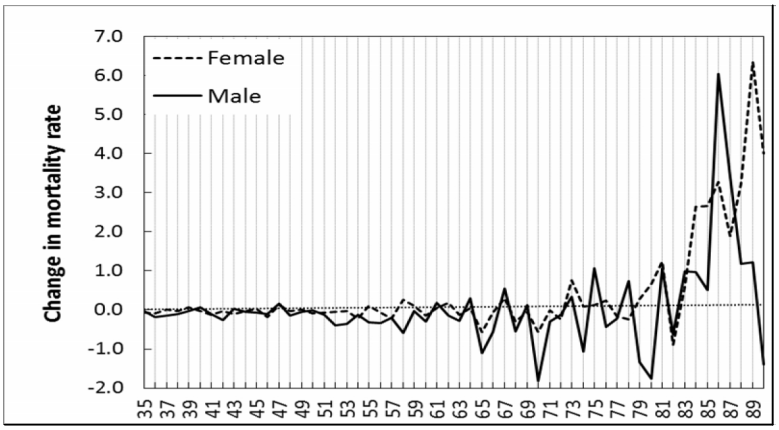

Fig. 4. Difference in age standardized mortality between 2012 and 2011

3.4 Single-year-of-age Differences in Admission via the Emergency Department

If the impact of the presumed infectious agent behind these events is via a sequential series of outbreaks from different strains of the same agent then it should be possible to demonstrate exaggerated saw tooth behavior between events in 2008 (when deaths peaked in England after the last outbreak/event) and the 2012 peak. To explore the fundamental impact of these events on admission to hospital via the emergency department Fig. 5 compares single-year-of-age standardized admission rates via the emergency department in England for 2012/13 versus 2008/09.

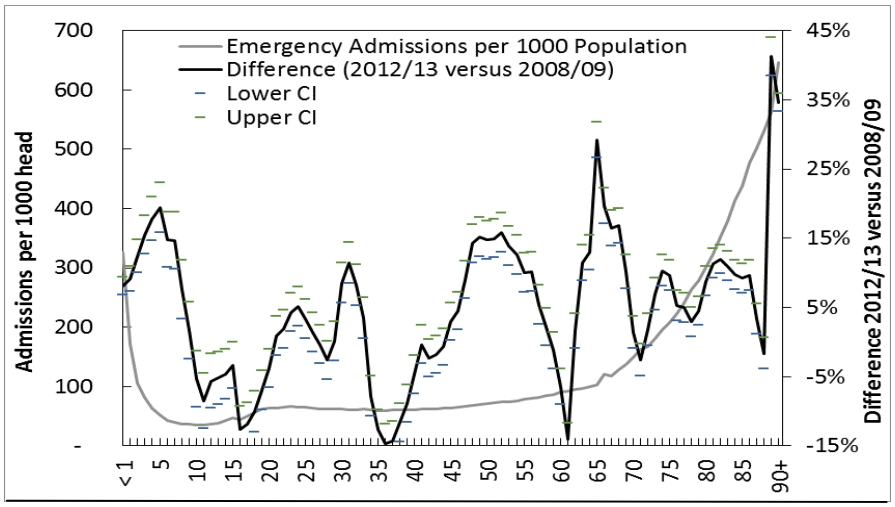

Fig. 5. Difference in admission rates between consecutive events/outbreaks

The 99% CI is displayed for each age and is relatively small due to the large number of admissions. On this occasion financial year data is only available, however, a March end to the financial year is not too different to a calendar year and as has been discussed above the impact of the event extended beyond 2008 into 2009. As can be seen the difference in

admission rates between the two peak years exhibits enhanced saw tooth behavior which is highly statistically significant.

Since this data has already been age standardized the saw tooth behavior is independent of differences in population between 2008 and 2012 and the most likely explanation is based on a fundamental shift in population health which appears to primarily occur via an immune mediated response as would occur in antigenic original sin. That the impact of these events is so profound that it explains the residual saw tooth behavior seen in 2011 in Fig. 3.

Hence by inference, the unexpected increase in deaths in 2012 appears due to an infectious agent with multiple strains and whose effect is predominantly against the elderly. Based on a process of matching between the diagnoses for hospital admission which specifically increase during these events and the clinical case studies for hospital admission due to cytomegalovirus (CMV) it has been proposed that there could be a potential role for CMV in these previously unrecognized infectious-like outbreaks [4,7,8,12-14,16]. The cyclical nature of infectious outbreaks is a well-known phenomenon (although with complex causes) and the cycle time is unique to each agent [18-19]. While CMV is a persistent agent cycles in the incidence of symptoms for another persistent herpes virus, herpes simplex (HSV), have been documented [20].

CMV is a ubiquitous herpes virus with an unusually large genome largely dedicated to immune evasion and subversion [12-14]. CMV exists as multiple strains of differing clinical significance and with super-infection of individuals [12-14]. Up until recently CMV was assumed to be largely innocuous except to the immune compromised, however, it has been pointed out that a wide variety of temporary to semi-permanent immune impairments exist in the so called immune competent population [12]. It has been suggested that up to 20% of the population, who are characterized by high levels of the inflammatory marker C-reactive protein (CRP) and/or by higher levels of CMV specific antibodies, may be susceptible to the more aggressive effects of CMV [13-14] and a number of potential genetic mutations have been observed to lead to the enhanced effects of CMV infection [12-14,21]. A role for active production of trained T-cells by the thymus is also possible [12-14,22].

In the proposed outbreaks the agent (CMV??) has only to cause an incremental change and the excess deaths arising from the 2012 event only represent less than 0.5% of the population aged 65+ and the increased admissions only represent 5% of this population [12-14]. These appear within the infectious capacity of this virus - were the effect to arise from the introduction of a new strain [12-14] and would be difficult to detect given the already high proportion of the elderly population who are CMV seropositive [23]. The clinical effects of CMV, especially resulting in death are also known to be greatest in the elderly [12-14,24] which is reflected in the process behind ageing and immunoscenescence which have been called inflammaging [25-27]. Further research is required to confirm the validity of the CMV hypothesis, but none the less the unexpected increase in deaths, hospital admissions, GP referral and emergency department attendances does require a cause consistent with the single-year-of-age behavior seen both in the deaths and medical admissions.

In the final section the issue of infectious spread will be addressed.

3.5 A Time Cascade of Deaths across England Originating in 2012

Analysis of both the 2008 and 2012 events using small area spatial units has demonstrated strong evidence for genuine infectious spread leading to large increases in medical

emergency admissions []. As was discussed in the introduction, deaths in 2012 were expected to continue to decline rather than show an unexpected increase. Hence the ratio of deaths in 2012 compared to 2011 will reflect the time at which the infectious spread reached a particular area. Areas showing a reduction in deaths in 2012 would then be expected to see an increase in 2013 as the spread eventually reaches that area. Evidence for this type of late arrival has been presented for the North East Essex region after the 2007 outbreak [6]. Such timing issues are addressed in Fig. 6 which gives a sense of spatial spread with time by looking at the rank for each LA with respect to the magnitude of the increase in 80+ deaths in 2012. Fig. 2 has demonstrated that the majority of extra deaths are in the 80+ age range hence this age group has been selected for analysis in Fig. 6.

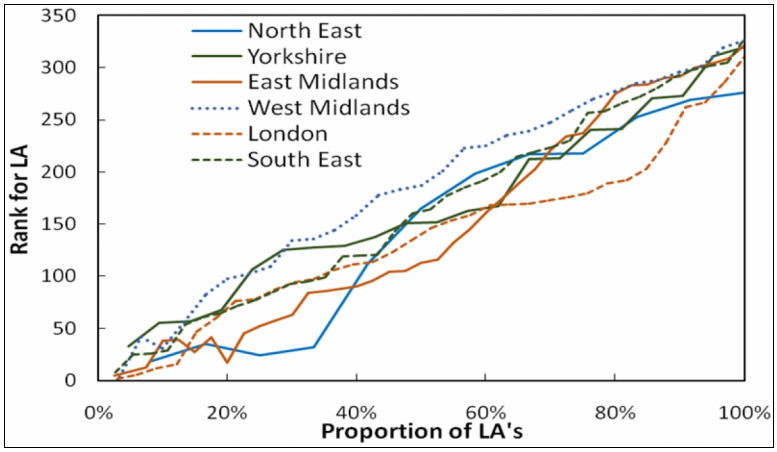

Fig. 6. Ranked change by local authority (LA) within larger English regions

To facilitate this comparison LA's have been grouped into larger government regions. Those LA's with a low rank do not exhibit an increase in 2012 and those LA's below a rank of 53 show a reduction in deaths. Such a reduction is entirely consistent with the expected ongoing reduction in deaths which would have been expected in the absence of the outbreak [1]. The remainder of the 274 LA's then show progressive increase in the deaths in 2012 consistent with variable timing of the onset in different locations. Hence low ranked LA's have not been touched by the infectious spread in 2012 while high ranked LA's will have experienced initiation very early in 2012. As can be seen from Fig. 6 London has 80% of LA's with a rank below 190 (indicative of late initiation) while at the other extreme West Midlands has 50% of LA's above 190 (indicative of more widespread early initiation). The North East has 33% of LA's below a rank of 35 indicating a significant cluster of very late initiating locations.

The impact of such spread across England is that the results in Fig. 4 are an underestimate of the full extent of the single-year-of-age specific effects since the difference has been diluted by a significant proportion of LA's which initiate in 2013 and later in 2012 rather than all LA's initiating early in 2012. A conservative estimate is that the difference between peaks and troughs in the saw tooth patterns is probably underestimated by around 40% due to this effect.

While it is appreciated that the full extent of the saw tooth behavior has been dampened by virtue of spatial spread across England Fig. 6 it should be possible to determine the point of

initiation for each LA using a monthly time series and conduct the before and after analysis for every LA pivoted around the point of initiation. The cumulative effect can then be summed across all LA's. The exact initiation date for each LA can also be cross-checked using the far more statistically significant and higher numbers of emergency medical admissions which are available at LA level [6,28].

4. CONCLUSION

An unexpected and large increase in elderly deaths occurred in England and Wales in 2012 and appears to be part of cyclic reoccurrences of a presumed infectious phenomena. Influenza can be excluded as a cause. The deaths and admission via the emergency department show very high single-year-of-age specificity which seems to indicate the involvement of the strain-specific effects of an infectious agent against immune function(s). Cytomegalovirus may be implicated as a causative agent or via opportunistic reactivation in response to another infectious agent. In addition to the obvious medical implications the single year of age effects have profound implications to the calculation of hospital standardized mortality rates (HSMR) and to the formula(s) used to distribute health care funding.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not required. Publicly available aggregate data.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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