A Previously Uncharacterized Infectious-like Event Leading to Spatial Spread of Deaths Across England and Wales: Characteristics of the most Recent Event and a Time Series for Past Events

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

Original Research Article

ABSTRACT

Aims: In 2003, 2008 and 2012, deaths in the UK showed unexpected and unexplained large increases similar in magnitude to the larger influenza epidemics seen before 2000. However there were no unusual levels of influenza to explain these spikes. This study aims to investigate the spread of a presumed infectious agent across England and Wales during the 2012 event, and to establish a longer time-series for these outbreaks.
Study Design: Longitudinal study of deaths.
Place and Duration of Study: Deaths for residents of Local Authority (LA) and regional areas in England and Wales from January 2009 to July 2014. Analysis of monthly deaths from January 1951 to December 2012 for the whole of England & Wales, to detect events prior to 2012. Analysis of calendar year deaths between 1963 and 2013.
Methodology: Running twelve month totals are used to detect the onset of a step-like increase in deaths which endures for twelve to eighteen months before abating.
Results: These events can be traced back to the early 1950's where they were intertwined with influenza epidemics. Moderately slow infectious-like spread across the UK occurs over a two year

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period. The last event which peaked in 2012 and 2013 led to a minimum estimate of 42,000 excess deaths, although 60,000 deaths are a more likely estimate. An additional event in 2010, which affects around 30% of LAs, appears linked with the swine flu epidemic and leads to underestimation of deaths in these locations for the 2012 event. The magnitude of the increase associated with the 2012 event decreased with increasing LA size, an effect which is due to the modifiable areal unit problem (MAUP). These events are always linked to large increases in emergency medical activity and emergency department attendances. The increase in deaths at local authority level is highly variable ranging from +5% to +30%, and this variability leads to large differentials in the cost pressures experienced by the local health services. In particular, 90% of LAs in London experienced the lowest percentage increase from the 2012 event. As a general rule it was observed that local authorities experiencing a low percentage increase in death for the 2012 outbreak, had experienced a high percentage increase following the 2008 outbreak and *vice versa*. This implies that the events are linked to the same agent.

Conclusion: The existence of a new type of infectious outbreak, with relatively slow spread, has been confirmed and is part of a longer time-series of outbreaks. Large numbers of deaths appear to be associated with each event, although the 2012/2013 event appears to have led to the highest number of deaths in any of these outbreaks since 1950. Urgent action is required since the next outbreak is due around 2016 to 2018.

1. INTRODUCTION

In 2012 deaths across the UK suddenly and unexpectedly increased with at least 23,000 'excess' deaths – the equivalent to a large influenza epidemic. This was a repeat of similar events which peaked in 2003 and 2008. No official explanation has ever been offered. However, infectious-like geographic spread at regional and local level has been demonstrated [1-10]. The extra deaths are age, gender and condition specific [7,11,12], and show particularly high increases for those with neurodegenerative and respiratory diseases [13,14].

Of particular relevance is the fact that that emergency department attendances and medical admissions show an equally abrupt increase at the point that deaths show these unexpected increases [15-18]. Also the gender ratio at birth shows a shift to higher male births at the point of onset of these infectious-like events [19], and to a more variable extent, GP referral to outpatients also increases [6]. Such trends are highly reminiscent of a recurring series of infectious outbreaks involving an agent leading to persistent infection, and the diagnoses involved appear to suggest some degree of immune mediation via the wide ranging roles of immune function in infection, inflammation and auto-immunity [1,20-21]. Each outbreak is accompanied by a cycle of financial surplus and deficit, which has been evident in the NHS in the UK and in the health insurance industry in the USA for many years [22,23].

It is well recognized that infectious agents, with an acquired immune response, exhibit a characteristic repeating time-series of infectious outbreaks [24]. This is best illustrated by the two sexually transmitted agents, gonorrhea and syphilis. The latter stimulates an immune response while the former does not. Syphilis exhibits an approximate nine year cycle in incidence, while gonorrhea has no discernable cycle [25]. The characteristic cycle time can be modified by immunization [26]. With over 1,400 agents known to infect humans [27], there is therefore the potential for undiscovered long-term cycles in both morbidity and mortality.

This study aims to characterize the infectious-like spread of the 2012 event across England & Wales, using a monthly time series of deaths at local authority level and to investigate likely dates for previous occurrences from the 1950's to the present. For consistency, the date used to refer to each outbreak will be the calendar year in which deaths peak across the UK, hence, the 2012 event actually commences in 2011 and extends into 2013 [8] but 2012 is the calendar year when the deaths peak.

2. METHODS

A monthly time-series of total deaths (all-cause mortality) for local authorities (LAs), counties and

regions in England and Wales from January 2006 to July 2014, was obtained from the Office for National Statistics (ONS). A monthly time series of total deaths in England and Wales from January 1951 to December 2012, was also obtained from the ONS.

Details regarding the ethnic composition and population density of each LA was also obtained from the ONS. The difference in deaths between 2009 and 2014 was calculated using the 2008-based components of change which were obtained from the ONS http://www.statistics.gov.uk/downloads/theme_population/snpp-2008/InteractivePDF_2008-basedSNPP.pdf)

A running 12 month total was constructed for each geographic area. Points at which unexpected step-like increases occurred, were determined using the successive ratio of deaths between 12 month periods. This method has been previously used to detect similar step-like increases in deaths, medical admissions and GP referrals in both the 2008 and 2012 events [3-6,8].

A running 12 month total of deaths will be subject to Poisson variation, where by definition, the standard deviation is equal to the square root of the average. On this occasion, the average is not known, but we have two point estimates for the before and after total deaths. The 95% confidence interval (CI) for the difference between before and after deaths was calculated in two ways. In the first, an approximation was used which was amenable to easy application in an Excel spreadsheet. In this approximation, the difference between before (B) and after (A) was considered significant if there was no overlap between B + 1.9 x √B and A – 1.9 x √A, i.e. where the two tails of the probability distributions did not overlap. The adequacy of this approximation was then checked using the online tool http://www.evanmiller.org/ab-testing/poisson-means.html#.

3. RESULTS AND DISCUSSION

3.1 Overview of Trends

As a general rule, deaths in England and Wales have been declining since the mid-1990s due to ongoing improvements in life expectancy, and are expected to reach a minimum around 2016 to 2017 before beginning a gradual increase, as growing population finally outweighs increasing life expectancy. However, the trends for individual LAs are more complex, and depends on past birth rates and inward immigration, especially for a series of new towns established in the 1940s and 1960s. Over the period 2009 to 2014, the Office for National Statistics (ONS) predicted up to a 15% reduction in deaths in Greenwich, Eden and Castle Morpeth, through to a 5% reduction for the whole of England. Around 45% of LAs were expected to show no significant change while only four LA were expected to show signs of an appreciable increase.

With these facts in mind, Fig. 1 demonstrates a running 12 month total of deaths for a variety of English LAs between Feb-10 to Feb-14. The period prior to the 2012 event has been included to demonstrate several key points:

- That this is not the only event leading to increased deaths
- Different LAs are showing variable trends over the period studied
- The majority of LAs go through a minimum of deaths (and associated medical admissions) in the 12 months prior to the outbreak (recall each point is a 12 month total)
- The timing and extent of the 2102 event varies between LAs

In a running total, a step-like increase in deaths creates a ramp-like feature, as successive months incorporate more of the higher monthly deaths into the running total, and this will be imposed on top of any underlying trends. Hence the ONS predicted a 10% reduction in deaths between 2009 and 2014 for Sandwell and this is reflected in the downward trend seen prior to 2012 for this LA in Fig. 1.

Several other events had the potential to affect the trend prior to 2012. Firstly, the 'swine flu' epidemic of 2009, which occurred in three waves peaking in Aug-09, Oct-09 and Jan-10 [28,29] will be part of the running total up to the 12 months ending Jan/Feb 2011. This was the first major influenza epidemic since influenza activity declined to a 100 year minimum around the start of 2000, see discussion in [1]. The trend shown in St Helens over this period suggests that this LA may have been disproportionately affected by the swine flu epidemic, while other locations appear to be far less so. Following the swine flu epidemic, influenza returned to very low levels of activity [28,29].

In addition, there was a period of extreme cold which occurred in December of 2010 [30,31]. Extreme heat/cold, i.e. large deviation away from 17 C, leads to increased deaths with extremes of heat being more detrimental [32]. For example, in a large Dutch study a -22 C or a +10 C deviation away from 17 C both generate around a 14% increase in daily deaths, although complex time lags are also involved [3]. The December 2010 period of extreme cold across the UK, only led to a 6% increase in deaths relative to the average for December over the previous five years [33], and will have a small effect on a running 12 month total.

There were local instances of lower temperature, and these will be reflected in specific LA trends. However such a 'spike' event will not create a ramp in a running 12 month sum but will create a plateau or 'table top' profile, i.e. a single high month works its way along the running 12 month sum, hence any effect on deaths will have been eliminated before the January 2012 running total.

Hence we have the situation that any increase seen from January 2012 onward is generally free from the effect of influenza or extreme temperature. However, any location experiencing a step-like increase prior to this point, may show under-estimation of the extent of the increase. In this respect, there is one major sub-group within this general rule, in that around 30% of LAs appear to undergo a step-like increase in deaths associated with the swine flu outbreak, and the impact of this feature in the running 12 month total does lead to underestimation of the following 2012 event. The details of this apparent influenza-triggered event will be discussed in more detail in section 3.6. However, for those LAs where the time-trend does not involve a significant response to influenza, Fig. 1 demonstrates a range of initiation dates (at the foot of a 12 month long ramp), a range of durations over which the maximum is maintained, and a range in the magnitude of the increase.
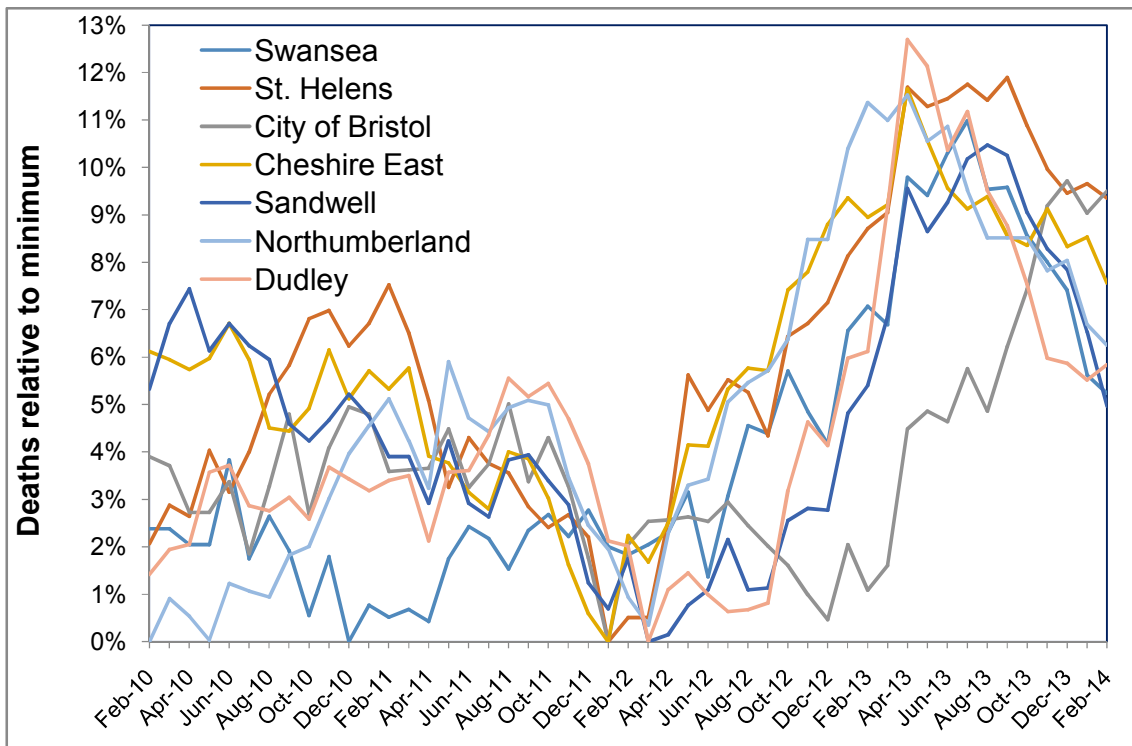

Fig. 1. Running twelve month total deaths for various local authority areas in England and Wales

Running 12 month total deaths are relative to the running 12 month minimum deaths. Note that for some LAs, such as Sandwell, deaths are trending down over time, while in others, such as Swansea there is a relatively flat time trend

3.2 Regional Trends

The point for the onset of a step-like increase, and the associated percentage increase in deaths for various regions and the larger counties are given in Table 1. Points to note are the range of dates, indicating progressive spread, and the variable extent to which different regions/counties are affected. The point of initiation for a whole region can be less precise due to infectious spread within the region, however, the initiation date given here is the point at which maximum step-like change occurred across the whole region, i.e. the point of greatest mass action within the LA. As can be deduced from Fig. 1 this may be the composite of trends from multiple LAs.

Granularity with respect to initiation date and percentage increase is evident, and will be even more pronounced at (smaller) local authority geographies. From a medical perspective this will translate into variable increases in emergency department attendances, medical admissions and health service cost pressures for which there is currently no recognition within the NHS funding mechanism [34]. In the absence of 'official' recognition that we are dealing with an infectious outbreak, the current NHS performance management framework interprets this as 'failure' to manage demand.

Table 1. Regional trends in increased death

Region	County	Date	Increase
EAST	Essex	Feb-12	5.2%
EAST	**Region**	**Feb-12**	**5.8%**
EAST	Hertfordshire	Feb-12	8.1%
EAST	Norfolk	Oct-12	5.1%
EAST	Suffolk	Jan-13	5.6%
EAST MIDLANDS	Lincolnshire	Feb-12	4.3%
EAST MIDLANDS	**Region**	**Feb-12**	**5.6%**
EAST MIDLANDS	Nottinghamshire	Feb-12	6.8%
EAST MIDLANDS	Derbyshire	May-12	4.3%
ENGLAND	**Country**	**Feb-12**	**5.0%**
LONDON	Inner London	Feb-12	1.3%
LONDON	**Region**	**Feb-12**	**3.7%**
LONDON	Outer London	Feb-12	4.9%
NORTH EAST	Tyne and Wear (M.C.)	Apr-12	4.6%
NORTH EAST	**Region**	**Apr-12**	**5.3%**
NORTH EAST	County Durham UA	Jun-12	7.3%
NORTH WEST	Greater Manchester (M.C.)	May-12	4.1%
NORTH WEST	Lancashire	May-12	4.4%
NORTH WEST	**Region**	**May-12**	**5.5%**
NORTH WEST	Merseyside (M.C.)	May-12	9.2%
SOUTH EAST	West Sussex	Feb-12	3.7%
SOUTH EAST	Kent	Feb-12	3.8%
SOUTH EAST	**Region**	**Feb-12**	**5.2%**
SOUTH EAST	Surrey	Oct-12	5.7%
SOUTH EAST	Hampshire	Oct-12	5.8%
SOUTH WEST	Cornwall	Feb-12	6.5%
SOUTH WEST	Devon	Feb-12	8.6%
SOUTH WEST	**Region**	**May-12**	**5.5%**
WALES	**Country**	**May-12**	**6.8%**
WEST MIDLANDS	West Midlands (M.C.)	May-12	6.6%
WEST MIDLANDS	**Region**	**May-12**	**7.0%**
WEST MIDLANDS	Staffordshire	May-12	9.2%
YORKSHIRE & HUMBER	West Yorkshire (M.C.)	Feb-12	2.7%
YORKSHIRE & HUMBER	**Region**	**May-12**	**3.8%**
YORKSHIRE & HUMBER	South Yorkshire (M.C.)	May-12	4.8%

Footnote: Data is for the largest counties within a region, M.C. = Metropolitan County (an administrative division of England covering large metropolitan areas)

3.3 Effect of Size

As can be appreciated from Fig. 1 and Table 1, the impact at a larger geography can be diminished due to progressive spread across that geography. The largest geographies should therefore experience the smallest *apparent* increase.

The effect of size has been illustrated in Fig. 2 by plotting the apparent percentage increase experienced in the step-like increase against the number of deaths just prior to the step-like increase. From the 400 geographical areas available for this study, only the 200 showing a statistically significant difference (95% Confidence Interval) between the before and after deaths are shown in Fig. 2. The average increase can be approximated by a series of power law equations. Hence for areas with 400 to 1000 deaths, the average increase (AI) = $1.804 \times N^{-0.393}$, 400 to 2000 deaths (AI = $2.456 \times N^{-0.439}$), 1000 to 10000 deaths (AI = $1.078 \times N^{-0.326}$), 2000 to 70000 (AI = $1.804 \times N^{-0.393}$), and >10000 deaths (AI = $0.09 \times N^{-0.046}$). These overlapping equations can now be used to adjust all areas to the equivalent increase for 1000 deaths, i.e. the most common number of deaths for an average sized LA just before the 2012 event.

3.4 Range in the Magnitude of the Step-like Increase

Granularity in the extent of the step-like increase (after adjusting for size) is evident in Fig. 3, where LAs have been grouped into larger regions. It can be seen that at local authority level, the effect upon size-adjusted deaths ranges from a modest 2.2% increase in Lambeth (Inner London, range for Inner London 2.2% to 9.2%), and a 2.5% increase in Richmondshire (North Yorkshire), to a 20% increase in Isle of Wight, St Helens & Knowlsley (Merseyside), Braintree (Essex), Mid Suffolk (Suffolk) and Bromsgrove (Worcestershire). There is no correlation between date of initiation and percent increase in deaths, and this would be expected from the known granular nature of infectious outbreaks, where transmission between persons and along social networks are known to be key to understanding the extent of spread [35]. London has a high proportion of areas experiencing an increase prior to Jan-12 in the running 12 month charts, and as discussed earlier, this may have acted to underestimate the increase for a proportion of the LAs in this location.
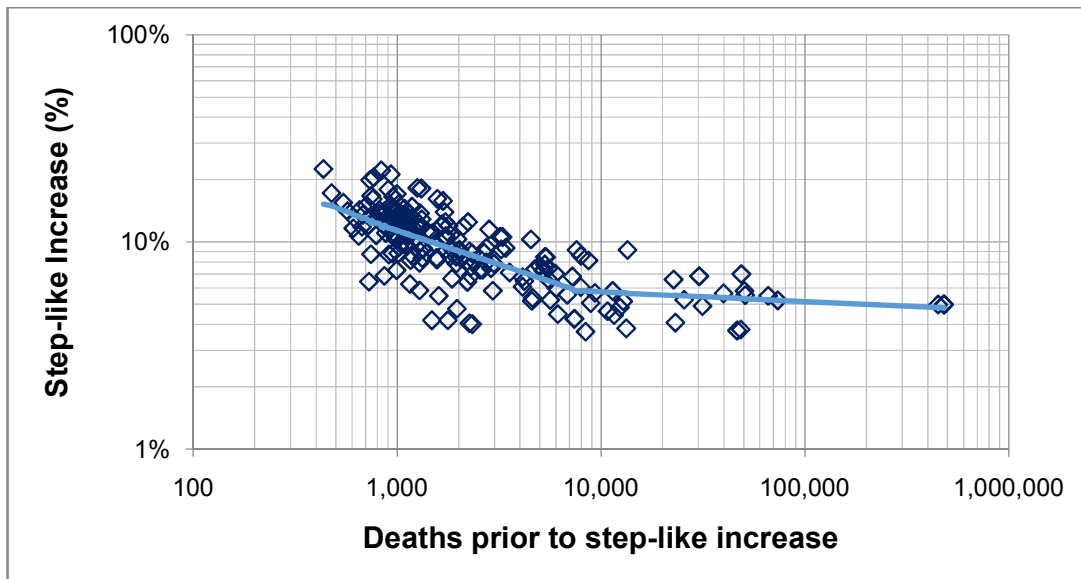

Fig. 2. Effect of size on the apparent value of the step-like increase
Data is for 200 LA/Regions where the difference between the before and after deaths is statistically significant at the 95% confidence interval
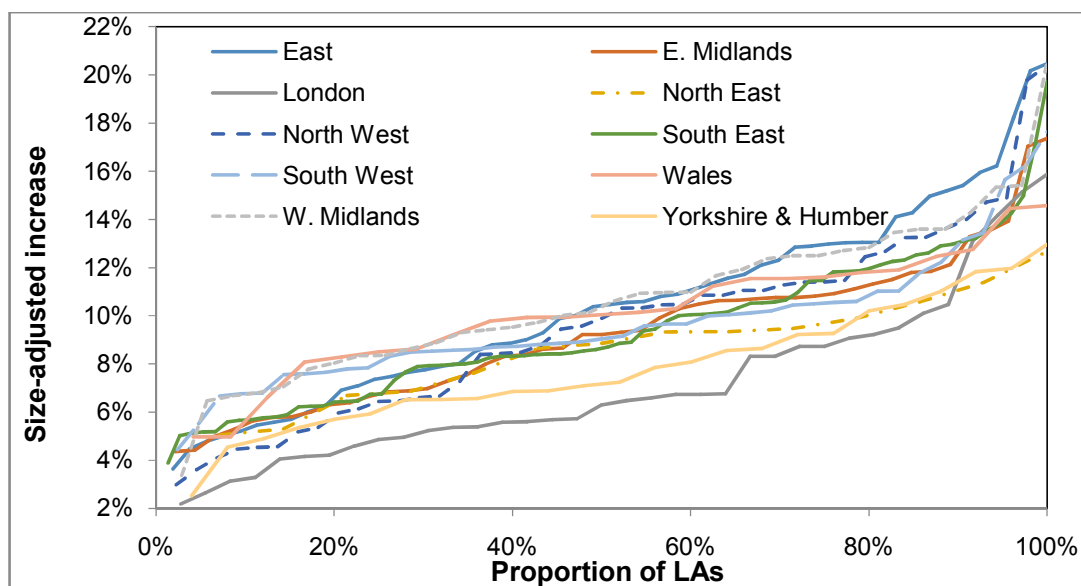
Fig. 3. Range in step-like increase for local authorities in England and Wales
Apparent increase has been adjusted to the equivalent at 1000 deaths per annum. Includes all 400 areas even if the increase was not statistically significant at the 95% CI. As a general rule any location with less than a 5% adjusted increase was below the 95% CI

As a general observation, LAs with the largest increase in deaths in 2008 experience the smallest increase in 2012 and *vice versa* (data not shown). This linkage is important because it establishes a cause and effect relationship between 2008 and 2012, i.e. these are not independent events but part of a wider time series (see later). It is this relationship between the successive outbreaks which probably explains why parts of Berkshire were so badly affected in the 2012 outbreak, with very large increases in medical admissions [5] creating operational difficulties in the local acute hospital [10].

3.5 Range in the Initiation Date

Issues of spread over time are explored in Fig. 4, where LAs have been grouped into larger regions. Fig. 4 shows the cumulative proportion of LAs experiencing the step-like increase in deaths and the time at which this occurred. First to initiate is one LA in the South East. However the South East is the slowest to reach the point at which 50% to 70% of LAs have initiated, and this does not occur until August 2012. On the other hand London experiences the most rapid initial spread, with 64% of LAs achieving maximum step-change by January 2012. However, after this point further spread is very slow, and the last LA does not initiate until April

2013. The results suggest that London had two loci, either in time or place, for eventual spread. On the whole, 35% of local authorities experienced the step-change in deaths in the interval October 2011 to February 2012. This step change endures for 12 to 18 months, hence the apparent large peak in national deaths during the calendar year 2012. Apart from large surges in spread in London during December 2011 and January 2012, there were three months (April, June, September) in 2012 where there were additional surges in spread which could be due to weather conditions or natural progression of infection along social networks [35]. The April surge corresponds to spread in parts of West and East Midlands and Wales, the June surge occurs in parts of the North East, Wales and the South East, while the smaller September surge is due to parts of the South East and London.

The unusual behavior in London is probably due to the fact that this region contains the most extreme gradients in poverty (including homelessness) and wealth, ethnic clusters, age (lowest national average age), social groupings and population density. Due to its higher population density, the London region therefore represents an ideal location to conduct further studies on the factors regulating the spread and extent of impact of these outbreaks.
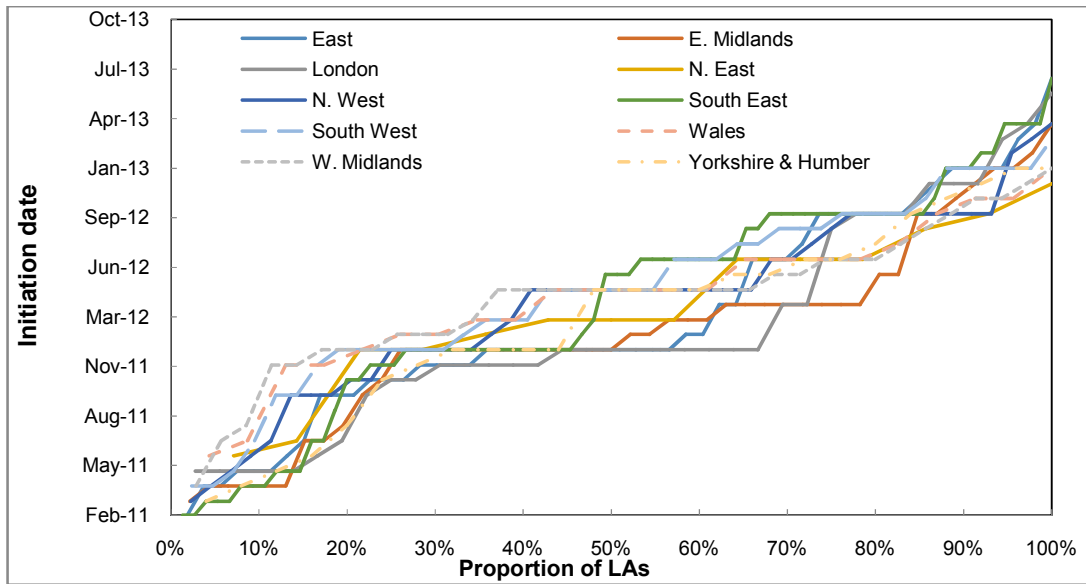
Fig. 4. Initiation dates for spread across England and Wales
Initiation dates prior to Jan-12 are provisional and may be subject to bias due to the limitations of the running 12 month methodology

In this respect a recent study in Berkshire has suggested that both the timing and the extent of impact is modified in areas with high Asian populations (mainly Pakistan/Bangladesh) [5].

The early commencement in February 2011 (Thanet, Kent), followed by a small cluster in April 2011 (Bromley, Thurrock, Adur), is consistent with the generally earlier initiation in Scotland [8]. Clearly much remains to be understood regarding these outbreaks. The early outbreak in Thanet is interesting due to what appears to be a very late outbreak associated with the 2008 event, where deaths stayed around 8% higher from May-08 to Nov-09 (data not shown). This extended period of a very high number of deaths may have acted to limit the impact of the 2012 event by virtue of previous death of a large proportion of the 'susceptible' population. Another late outbreak associated with the 2008 event has been demonstrated in North East Essex, and was associated with a surge in health care costs leading to a large financial deficit [3].

The possibility that the percentage increase may be influenced by the proportion of older people was investigated, with an average increase of around 5% for LAs with less than 9% aged 65+ climbing to an average of 10% for LAs with more than 15% aged 65+ (data not shown). This relationship probably explains the lowest average

increase seen for London in Table 1 and Fig. 3. To an extent, this age effect will partly be due to lower rates of death and admissions observed in younger age groups associated with these outbreaks [3,5-6,9-10], plus the possibility that some degree of elderly to elderly interaction may be involved. An earlier study suggested that GP surgeries may be inadvertent loci for the spread of the agent [3].

3.6 Estimates for Total Deaths Due to the Outbreak

3.6.1 Running 12 month methodology

The use of monthly data has allowed the point for the onset of the step-like increase in deaths to be identified with a degree of precision in 50% of LA, and with potential uncertainty in the other 50%. The increase in admissions (after adjusting for size) is likewise accurate (95% CI) for 50% of LA, while 25% of LA with an initiation date before Jan-12 are probably underestimated. The final 25% also appear underestimated due to unusual trends in deaths not anticipated in the ONS forecasts, and which appear to be associated with an influenza-triggered event which also created a step-like increase in deaths (see section 3.6).

Despite the likely underestimation in half the data the measured increases can be used to gain an

estimate for the extent of increased deaths arising from the outbreak. Hence a count of extra to expected deaths for England & Wales is thereby increased to a 'minimum case' figure of around 42,860 extra deaths (spread across 2012 and 2013). See 3.5.2 for an estimate using alternate methods for England and Wales. Given the fact that there is further granularity in onset and increase between small areas within each LA [3-5], a reasonable estimate for total deaths across the entire UK attributable to the 2012 outbreak is likely to lie somewhere above 60,000 deaths. It would appear that we are dealing with an event of huge public health significance.

3.6.2 Alternative methods

A more traditional approach to estimating the excess deaths would be to compare actual deaths against expected deaths, either using some form of trend line or a more formal methodology such as the components of change used by the ONS. Table 2 therefore shows actual deaths in 2012 and 2013 for the whole of England and Wales, compared to the 2008-based ONS components of change forecasts and a polynomial curve fit based on a series of annual deaths from 1963 to 2013. The trend for males and females were determined individually (after exclusion of the high years associated with the outbreaks) and combined to give total expected deaths.

As can be seen in Table 2, the ONS methodology tends to underestimate deaths by around 2,891 deaths per annum, and the calculation of extra deaths in 2012 and 2013 has been adjusted to reflect this bias. The adjusted ONS methodology gives 5,294 extra deaths in 2010 (see Section 3.6) and a combined total of 45,063 excess to expected deaths in 2012 and 2013. The polynomial method gives 4,468 extra deaths in 2010 (after adjusting for -3,734 in 2011), and gives a total (after adjustment) of 44,935 excess to expected deaths in the two years. Both of these figures are comparable to

the (under) estimate derived from the sum of all LAs given in 3.5.1.

A total of 45,000 deaths arising from an infectious event is somewhat alarming, and given that this is an underestimate, the public health significance of this (unrecognized) outbreak cannot be over emphasized.

3.7 An additional Event Apparently Associated with Influenza A (H1N1)

With over 1,400 known human pathogens (>200 viruses) [27] it would be surprising if the outbreaks identified in this study were the only infectious outbreak occurring during the study period. In this respect the swine flu (Influenza A (H1N1)) epidemic occurs in the middle of the study period. This epidemic commenced around April 2009 and reached pandemic phase by around June 2009. In the UK this outbreak occurred in three waves peaking in Aug-09, Oct-09 and Jan-10 [28-29] and influenza A (H1N1) is also known to be associated with the onset of severe cardiac dysfunction in adults [36]. Influenza has also been proposed to leave residual viral regulatory particles with unknown pathological consequences [37]. Fig. 5 investigates the potential knock-on effects from H1N1 in England and Wales, by investigating a group of LAs which appear to experience a step-like increase in deaths triggered by the swine flu epidemic.

In Fig. 5 the top 20 LAs have been aggregated and the time profile for Slough is shown separately. Slough is included because it has independent verification of the effect of the 2012 outbreak on hospital medical admissions [5]. Hence in this LA there was no apparent increase in medical admissions associated with the increase in deaths which commences in Oct-10 Fig. 5, but there is a large increase in medical admissions which initiates around Sep-11. However, the effect on deaths are largely obscured by the earlier Oct-10 step increase.

Table 2. Estimates for extra deaths in 2012 and 2103

Calendar year	Actual deaths	ONS prediction	Polynomial prediction	Extra to ONS minus 2,891	Extra to polynomial
2010	493,242	485,057	492,508	5,294	734
2011	484,367	481,476	488,101	0	-3,734
2012	499,331	478,655	484,145	17,785	15,186
2013	506,790	476,621	480,775	27,278	26,015

Hence while the running 12 month methodology has successfully detected the potential influenza-associated step-increase, which has inadvertently obscured the effect upon deaths in the approximate 30% of LAs where this event occurs. To investigate if this event is genuinely associated with the swine flu epidemic, Fig. 6 investigates the timing of the step-like increase in the 70 LAs with the largest percentage increase at this time. As can be seen, initiation ranges from Jun-09 to Dec-10 which covers the beginning of the pandemic phase, through the third (and largest) wave in the UK around Jan-10, and extending for another 11 months, during which the virus is presumably still circulating in appreciable numbers. Note that the majority of LAs initiate in Jan-10 during the third wave.

However, we now have several unanswered questions, namely, why the apparent absence of the increase in deaths in over 100 LAs, why the increase in death but not medical admissions in Slough, and why the tail of initiation dates through to Dec-10?

It is now known that prior receipt of 2008/09 trivalent inactivated influenza vaccine was associated with increased risk of medically attended H1N1 illness [38], and 2008/09 influenza uptake patterns in the UK are likely to vary significantly between LAs.

Secondly, like all outbreaks, influenza shows spatiotemporal patterns of spread and incidence [39]. This may have been further compounded by higher than usual inward immigration from the core EU countries during the whole of 2010 as economic hardship in countries such as Greece, Italy, Spain and Portugal led to high unemployment [40].

Thirdly, re-examination of the data covering medical admissions in Slough [5] shows that small-area infectious-like spread of an agent, does indeed occur between Nov-09 and Jun-10. However, the spread in initiation dates leads to most of the small-area trends cancelling each other out when the data is aggregated for the whole of the Slough LA. Hence medical admissions, as well as deaths, were indeed affected. However, the following 2012 event is characterized by a far greater increase in medical admissions than deaths.
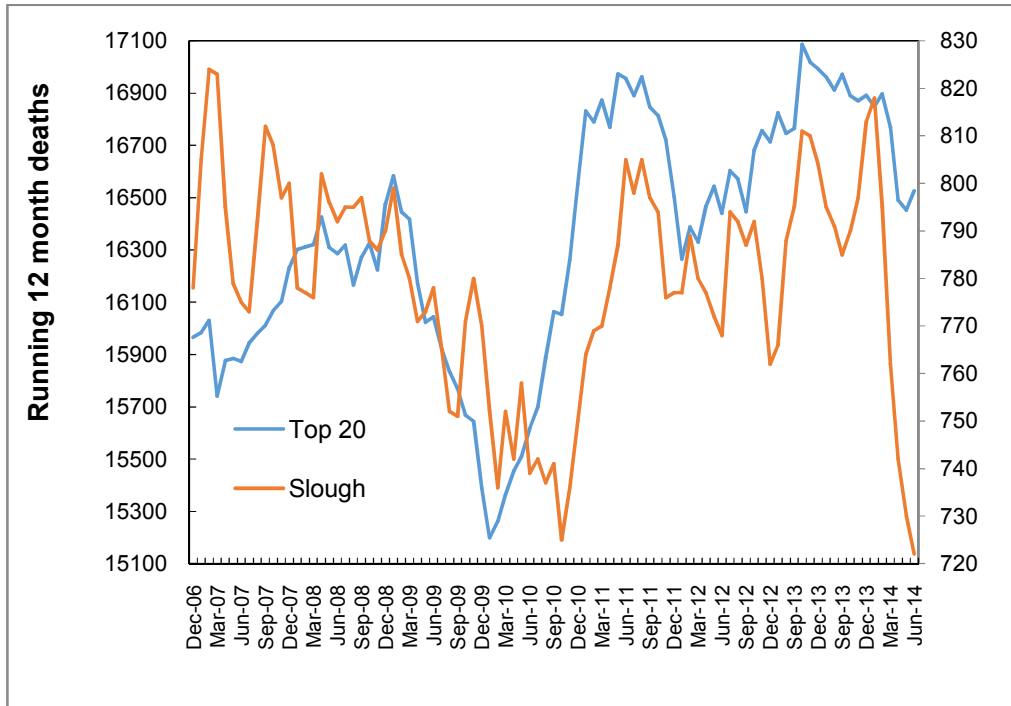

Fig. 5. Trend in deaths for the 20 local authorities experiencing a large influenza-triggered step-increase in deaths

The top 20 LAs (left hand axis) all experienced greater than a 13.5% step-like increase in deaths which initiated around January and February 2010. Data for Slough (right hand axis)
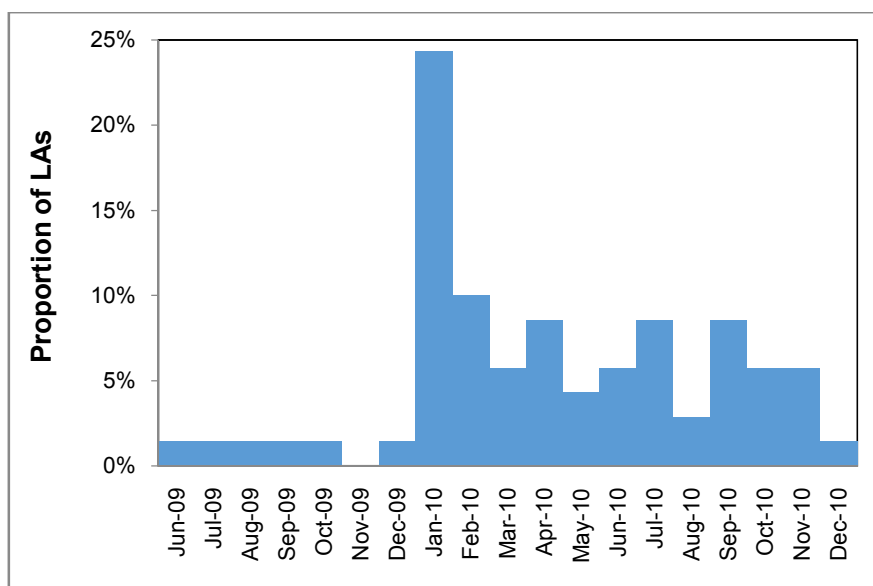
Fig. 6. Initiation dates for the potential influenza-initiated event
Initiation dates are for the 70 LAs experiencing the highest increase in deaths (>9% increase) for the potential influenza-initiated event

Further study of the LA data, shows that the large increase in deaths associated with the 2010 event *never* occurs in LAs with high ethnic populations, i.e. the target population appears to be white British, and the large increases do *not* occur in LAs with very high population density, i.e. not among the deprived. One possible explanation, could be related to international travel, which is likely to be more prevalent in affluent populations coupled with variation in vaccination rates.

Influenza appears to be highly implicated either as cause or precipitating agent, and this appears to be the first study identifying this potential role for H1N1, on a period of increased death lasting for around 12 months after initiation. In its own right, this additional infectious outbreak deserves greater attention.

In summary, around 30% of LAs are badly affected by the 2010 event, and this leads to gross underestimation of the impact of the 2012 event (when using the running 12 month methodology). Use of medical admissions, especially for small-areas, is less prone to this bias, and should always be coupled with any study on deaths.

3.8 A Time Series for Past Outbreaks

All infectious outbreaks have their own unique periodicity, and the possibility that these events are part of a far longer time-series will now be explored. To illustrate this issue Fig. 7 shows both the 2008 and 2012 outbreaks for the county of Devon in South West England.

Devon has been chosen because it is one of the 45% of locations where there is no downward trend in deaths over the time period, as was seen for some LAs in Fig. 1, and because the 2010 event is of minor significance in this location. Devon is a popular retirement location with total population of retirees limited by the availability of suitable housing for inward immigration of a relatively prosperous retirement age population. Death of a retiree therefore creates a space for another inward arrival, and hence the trend over time remains relatively flat and can be considered to be an example of sampling with replacement.

However, the initiation of a smaller increase in deaths due to the 2008 outbreak, can be seen to commence around Sep-08, while the larger 2012 outbreak commences around Feb-12. This confirms the result of earlier analysis which suggested that the 2008 outbreak was smaller in magnitude than the 2003 outbreak [7]. However, somewhat curiously, the 2008 outbreak led to a far higher impact on GP referral than on medical admission [6].

Similar analysis can be conducted using monthly data for the whole of England and Wales, and

the results of this historic analysis are presented in Table 3, along with relevant comments regarding other health and health service characteristics which are seemingly linked to these outbreaks.

Due to the fact that the outbreaks are entwined with several large influenza outbreaks in the period before 2000, an attempt has been made to cap the worst of the influenza spikes in the data analysis. A similar method has been used in a previous study of the trends in death in Scottish Area Health Boards [8]. A running twelve month total was then constructed searching for the points of a 12 month long ramp to indicate the composite point of initiation across all of England and Wales. Events with a table top profile are excluded, since by definition they arise from a spike event such as a seasonal influenza outbreak.

An infectious outbreak of this magnitude would not be confined to the UK, and Fig. 8 explores the possibility that the costs of health care in the USA are strongly influenced by these outbreaks. In Fig. 8, health care costs are relative to Gross Domestic Product (GDP) as a way of adjusting the data for inflation, while the use of a third order polynomial attempts to adjust for growth in the health care sector over time. See the study by Borne and Santerre [41] for an alternative view of the impact on health care insurance costs and premiums using direct adjustment for inflation.

While the consequences of the outbreaks from 1993 onward can be confirmed using hospital admission data, the position before this is less clear. Detailed cost data is only available from 1960 onward in the USA Fig. 8, and hence Table 3 collates information from a variety of sources to derive a time series of outbreaks from 1951 onward. On some occasions the increase seems greater in the US, which could partly be due to the limitation of using whole year data or due to the interaction with the weather or seasonal influenza. However, the availability of these dates should allow researchers to look for patterns of disease using the time series periodicity. Note that costs in the USA show an extended period of higher than average behavior during times when there are a series of outbreaks at generally closer intervals, hence the very large peak between 1986 and 2000.

Note also that the onset of the effect upon total costs in the USA usually lags behind the UK by around one year, except in 2001 where a slightly earlier increase occurs followed by an increase in 2002 in the UK. There is no specific reason why an outbreak could not originate earlier in the USA, although as has been observed in the UK the outbreak generally initiates earlier in Scotland [8-9]. It is highly recommended that future research focusses on more accurate daily count of deaths [52], linked with the higher numbers of medical admissions which accompany these outbreaks.
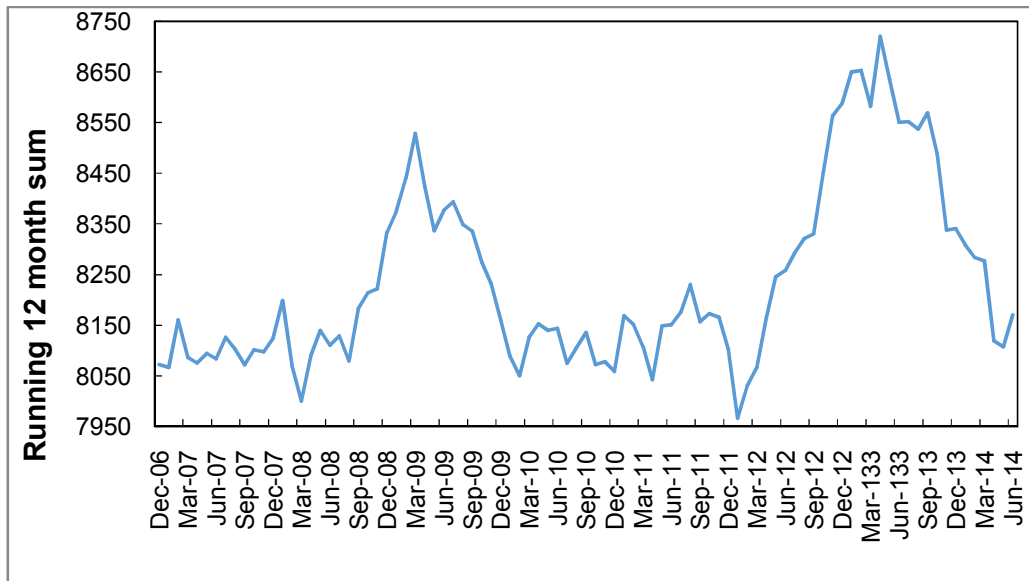

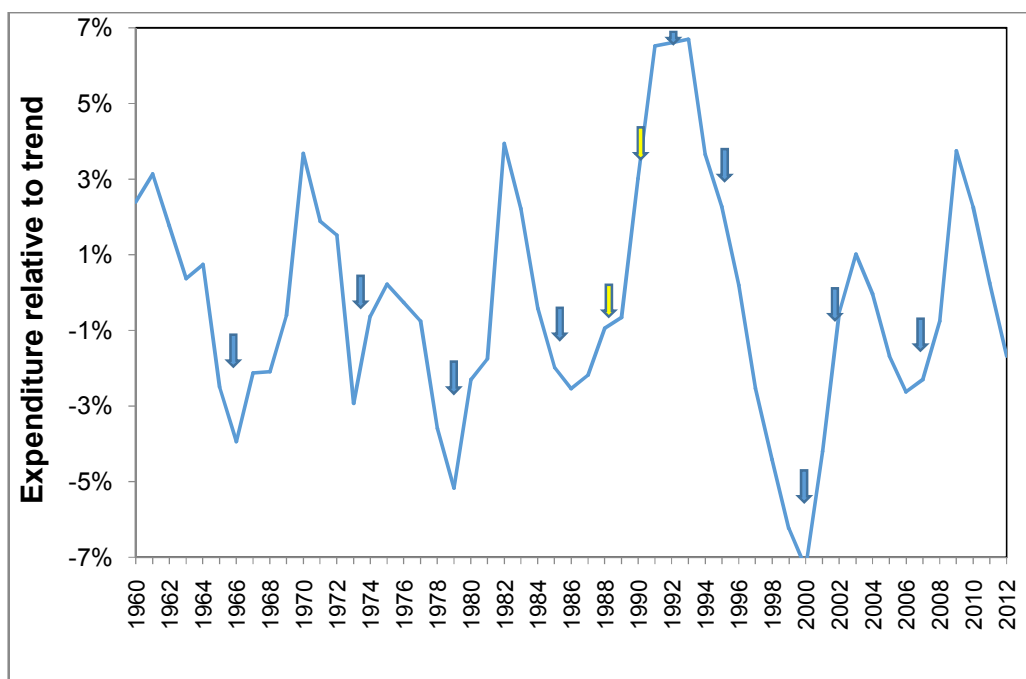**Fig. 7. Effect of 2008 and 2012 outbreaks on total deaths in Devon**

Fig. 8. Total health care costs in the USA as a percentage of GDP relative to trend
US total health care expenditure as a percentage of gross domestic product (GDP) is from
http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-
Reports/NationalHealthExpendData/NationalHealthAccountsHistorical.html The time-series has been
approximated by a third order polynomial and the actual is relative to the polynomial trend. The arrows mark the
approximate dates for the outbreaks in the UK. The two arrows with yellow fill appear to show partial effects in
the UK

Table 3. Likely dates for the outbreaks based on trends in death and other health associated behavior

Date	Comments and related knock-on effects
1954	Increase in deaths in England & Wales (E & W) starts around Apr-54.
1957	Increase in deaths in E & W starts around Aug-57.
1960	Increase in deaths in E & W starts around Mar-60; total health care expenditure in USA reaches a maximum around 1961, probably magnified by the three-in-a-row outbreaks in 1954, 1957, 1960 (see Fig.8).
1965	Increase in deaths in E & W starts around Feb-65; increase in total healthcare costs in USA commences one year later.
1974	Increase in deaths in E & W starts around Feb-74 (unclear); increase in total health care costs in USA commences in 1975. Small peak in deaths across the whole of the UK.
1978	Increase in deaths in E & W starts around Apr-78; the gender ratio in E & W reaches a minimum [19]; increase in total healthcare costs in USA commences in 1980. Broad peak in deaths across the whole UK in 1978 to 1980.
1985	Increase in deaths in E & W starts around Apr-85; the gender ratio in E & W reaches a minimum [19]. Increase in costs in US commences in 1986 or early 1987. Broad peak in deaths across whole of UK in 1985 and 1986.
1987	Some evidence for a possible increase in deaths in (perhaps parts of) E & W commencing May-87; start of a weak peak in the gender ratio; some evidence for a shoulder in the USA. Maximum deaths across the whole UK in 1988 and 1989. ED attendances in England show a step-like increase [42] and the size of the inpatient waiting list in England peaks (a by-product of bed and cost pressures) [43].
1991	Some evidence for a possible increase in deaths in (perhaps parts of) E & W commencing Sep-91; start of a weak peak in the gender ratio [19]; some evidence for a shoulder in the USA. Modest peak across the whole of the UK in 1991. Possible weak outbreak or effect due to influenza – requires clarification. The size of the inpatient waiting list in England starts to increase [43].

Table 3 continued ……

1993	Increase in deaths in E & W starts around Feb-93 while this marks the point of maximum increase in Scotland [8-9]; the gender ratio at birth in E & W reaches a minimum [19]. Increase in costs in US reaches a broad maximum. Large increases in emergency medical admissions documented across the whole of the UK. ED attendances in England show a large increase [42]. The size of the inpatient waiting list peaks in late 1993 [43].
1995	Increase in deaths in E & W starts around Feb-95 and this is near to the point of maximum increase in Scotland [8-9]; the gender ratio in E & W reaches a minimum [19]. Costs in the US show a shoulder. ED attendances in England show an increase [42].
1998	Increase in deaths in E & W starts around Jan-98 while this is near to the point of maximum increase in Scotland; the gender ratio in E & W reaches a minimum. Costs in the US show a shoulder. This three-in-a-row series of outbreaks leads to numerous studies into what is perceived to be an 'unsustainable' increase in emergency admissions observed in many countries. ED attendances show a step-like increase in the 1999/00 financial year [42]. The size of the inpatient waiting list peaks in late 1998 [43].
2002	Increase in deaths in E & W starts around Sep-02 while the point of maximum increase in Scotland is in Aug-02; the gender ratio in E & W reaches a minimum [19]. Increase in costs in US reaches a broad maximum. Costs in the US appear to start to increase in 2001 but do not peak until 2003. ED attendances increase [42]. Initiatives to dramatically reduce inpatient waiting time dampen the effect on the size of the inpatient waiting list [43].
2007	Deaths in E & W start to rise around Aug-07 although maximum increase in Scotland is around Dec-06; the gender ratio in E & W reaches a minimum [19]. Costs in the US show a large increase in 2008 and again in 2009. Emergency department attendances and medical admissions in England rise [1]. GP referrals show a large increase [6] along with changes in the ratio of follow-up appointments [44]. ED attendances increase [45-47]. Primary Care Organization costs rise in a manner reminiscent of spatial spread [48-50]. Hospital bed occupancy likewise increases showing spatial spread [49].
2012	Deaths in E & W start to rise toward the end of Feb-12 while deaths in Scotland show the largest step-change in Mar-12 (although increase can be seen in some Health Board areas around mid-2011) [8-9]. Emergency department attendances, medical admissions and GP referrals all rise in England [45-47,51]. Large peak in deaths across entire UK and in 2013. Bed occupancy increases [10]. Costs in the US have reached a minimum in 2012. As at May-13 insurance premiums were continuing a trend of declining increases, however, this is a classic sign that the next turn of the health insurance underwriting cycle is about to begin.

Deaths in England and Wales are from the author's analysis of a monthly time series of data from the Office for National Statistics (ONS). Data from the USA as per Fig. 6 with additional analysis based on supplementary material from the study of Born & Santerre [41]

To confirm the dates presented in Table 3, a polynomial curve fit has been performed on calendar year deaths from 1963 to 2013, and actual versus expected (from the curve fit), are displayed in Fig. 9. These figures have not been adjusted for the impact of any influenza outbreaks or severe winters.

The outbreaks in 1993, 2003, 2008 and 2012/2013 can be clearly seen, and the magnitude of the 2012/2013 outbreak can also be appreciated. The only other event to account for such a large increase in deaths can be seen in 1963. This peak was due to a two month period of extreme cold (the worst in 200 years) from January to February 1963 [53], which will have acted to exacerbate winter respiratory infections at a time when central heating was not common in the UK.

The cluster of outbreaks occurring from 1995 to 1999, can also be seen as a run of above average deaths arising from the fact that most of the outbreaks commence in mid-year and take around two years to fully spread across the UK.

Proposed outbreaks in 1965, 1978 and 1985 all show as high deaths over two years 1965/1966, 1978/1979 and 1985/1986 respectively. The 1991 outbreak (possibly partial spread), shows as a small peak. The proposed 1987 outbreak seems to be overshadowed by the 1985/1986 double peak and requires further study to fully validate.

The situation between 1968 and 1978 is confounded by the arrival of the Hong Kong flu in 1968, and during this interval there were about 120,000 excess deaths. The study of Tillett et al. [54] concluded that for these 120,000 deaths about 82% were estimated to be in those aged 65+ years, 17% in the 40-64 year age group and 1% in younger adults. Of these, 67% were respiratory disease and 31% circulatory system disease. Respiratory deaths increased in all age groups during an epidemic, but of the deaths certified as due to circulatory disease,
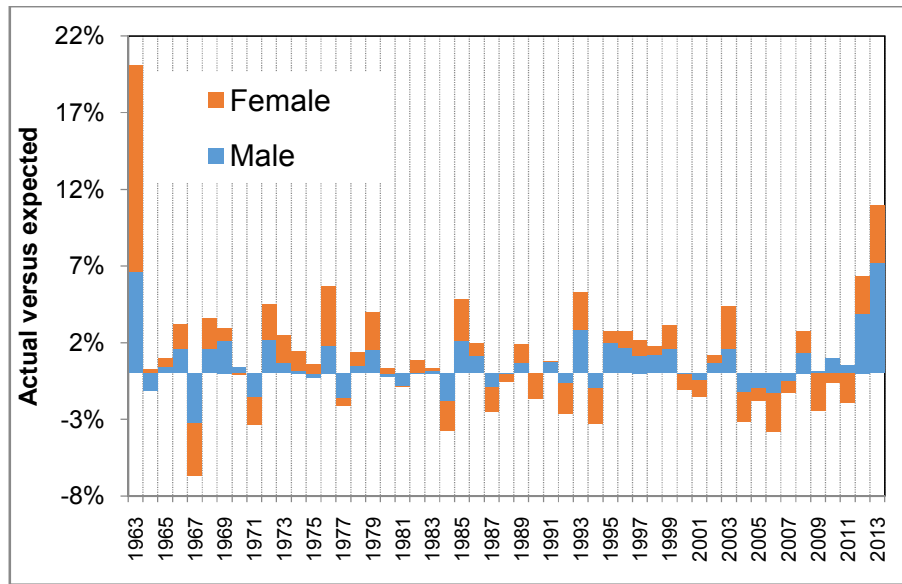
Fig. 9. Trend in actual versus expected deaths
Expected deaths are from a polynomial cure fit (4th order for male and 5th order for female)

cerebrovascular deaths were mostly in the 65+ age group, and ischaemic heart disease deaths in the 40-64 year age group. In this 40-64 year age group there was evidence that the effects of cold weather and epidemic influenza were multiplicative rather than additive. During the worst influenza winter of 1969/70, respiratory deaths increased by approximately 55% and circulatory system deaths by 4%. Deaths in the elderly increased by 10%, in those aged 40-60 years by 8% and in younger adults by 4%. Hence the Hong Kong flu accounts for the two peaks in 1968 and 1969.

In retrospect, it has been proposed that an outbreak of the proposed agent before an influenza outbreak leads to enhanced deaths during the following influenza outbreak [3]. Hence the conclusions of Tillett et al. [54] probably require a degree of re-evaluation regarding the exact contribution of influenza to the deaths and the cause of death.

One of the more interesting conclusions from the study of Tillett et al. [54] was that there was no evidence that excess deaths are followed by a deficit during the following year. This is largely due to the fact that excess deaths are typically less than 0.7% of the live population (aged 65+), and so do not make an appreciable impact on the pool of live persons [14]. This is important because the dip in deaths (and medical admissions) which almost always occurs before one of these outbreaks, seems to be a real

indicator of an impending outbreak. In this respect the large minimum in 1967 before the arrival of the Hong Kong flu in 1968, suggests that the 1968/1969 double peak may have hidden one of the outbreaks. It would seem that a far more detailed re-examination of past trends in deaths is warranted.

The authors own unpublished analysis of monthly trends in deaths for a variety of European countries, shows clear evidence for the 2012 event in at least 9 countries other than the UK, and evidence for something similar to the outbreak imposed on top of a spike event (possibly seasonal influenza/respiratory viruses), in a range of other countries. The first country to show a step-like increase is Malta (one of the world's smallest and most densely populated countries) in Nov-11. In 2011 the population of Malta was around 420,000 with around 3,000 deaths per annum, which is about the equivalent to three average sized English LAs. Given the close historic ties with the UK and the large volume of holiday traffic between the two countries, the Nov-11 initiation is within that experienced in the UK. Both the 2003 and 2008 outbreaks can also be seen in the time series of deaths for Malta.

3.9 Wider Discussion

The method of running 12 month totals to detect a step-like change is fairly robust within the limitations of a simple methodology. However, in

an area as large as a local authority, it is unlikely that an infectious outbreak will occur simultaneously in all parts, and high granularity in terms of initiation date and percentage increase in medical admissions has been demonstrated for small areas within a local authority [3-5]. This study has used the point at which the maximum value of a step-like change has occurred, i.e. there may be evidence for an increase in deaths at locations within the LA before the point of maximum increase. However for consistency all reported months for initiation are for the maximum change.

Due to the fact that the number of deaths in a number of LAs are expected to decline through to 2015 [5], the calculated step-like increase for some LAs may therefore be slightly underestimated by a maximum of 1% to 2%. A correction factor was therefore applied in this study.

An additional source for underestimation of the value of the step-like increase, lies in the fact that the running 12 month total method relies on a comparison of two 12 month totals either side of the step-like increase. The infectious outbreak which is the focus of this study, is only one among many, and therefore any other unusual infectious outbreaks, i.e. apart from the normal level of winter infections, occurring in the 12 months before the step-change, will lead to underestimation of the step-change. This study can therefore be regarded as a conservative estimate. It has already been proposed that these outbreaks act to amplify the effects of seasonal influenza later in the year [3], however this should be seen as a 'normal' consequence of these outbreaks, and is not evidence for over-estimation. Future studies will therefore need to isolate those LAs where the above two sources of underestimation are significant.

While these outbreaks seem to occur most commonly at a frequency of two per decade, Table 3 notes several periods of three in a row occurrence. There is some evidence for an outbreak-like occurrence in 2010 in some LAs similar to the single MSOA observed in a study of this outbreak in Berkshire [5] and influenza A (H1N1) seems to be implicated. Several other LAs appear to respond to the 2008 event with a seeming permanent increase in deaths. Further studies therefore need to employ more sophisticated methods to untangle some of the more complex outcomes which could arise out of

these outbreaks, and/or more complex trends in deaths which may occur in some LAs over time.

Limitations of the method aside, the evidence has been gradually accumulating to demonstrate the existence of a previously uncharacterized type of infectious outbreak with a unique time-pattern of spread. The same spatial spread has been demonstrated to also affect GP referrals and medical admissions [1,3-7], and has been characterized at both larger regional level and smaller LA level in Scotland [8-9].

While the study of the statistical evidence for such an outbreak has been required to establish cause and effect, it is now an imperative that research switches to a deeper understanding of the profound effects upon certain medical conditions. In this respect, seeming time cascades for admission to hospital for particular conditions have been characterized on three occasions [3-6]. The causative agent has been proposed to work via immune modulation [1,20-21], and hence depending on the sensitivity of particular conditions to infection, inflammation and autoimmune processes, a time cascade for the hastening of particular diseases would be a logical outcome. Indeed admissions for the more aggressive forms of tuberculosis appear to peak some three years after each outbreaks [56] while those for allergy peak after about one year [57].

The agent responsible for these outbreaks is presumed to be reasonably difficult to transmit by virtue of the extended time over which spatiotemporal movement occurs. However the relatively rapid step-like increases which appear to occur at local level, also imply that some form of mechanism exists for the creation of local mini-epidemics [3]. A study of medical admissions at a large acute hospital in Berkshire following the 2012 outbreak, shows that respiratory admissions, in general, and admissions (and deaths) for pneumonia, in particular, show a very large step-like increase during the outbreak [10]. Transmission via respiratory aerosols (under an appropriate set of conditions?) therefore appears to be one route for transmission [3,14].

The immune modulating herpes virus, cytomegalovirus (CMV), has been proposed as a potential candidate [1,7,13,20-21]. However, further research is urgently required to establish if this is the actual causative agent. An alternative possibility is that the range of CMV-like diagnoses are due to re-activation of existing

CMV strains within the population in response to infection by this other agent.

The external validity of this study will therefore be modified by the specific factors regulating spread of this agent and the size of the geographic entity. For example, in the USA, the far larger geography, lower general population density, and greater distances between towns and cities, will imply slower spread and possibly instances of lower percentage increase. Ethnic origin (specific genetic variants) also appear to play a role.

The number of deaths *per se* rather than standardized mortality rates, are an important part of health care costs [52,55,58-59]. For example, an Australian study has demonstrated that in the last year of life, 83% and 85% of persons had at least one ED attendance and one hospital admission respectively [60]. The effects on health care costs is of equally profound importance given the high granularity in both timing and percentage increase in deaths. It is important to stress that the effect on total costs is far wider than just end-of-life costs, and there are even larger increases in emergency department attendances, medical admissions, occupied beds, plus increased GP referral and the impact on primary care costs [42,45-47,51,61-69].

4. CONCLUSION

In England, the link between infectious outbreaks and health service funding has been effectively ignored, and costs are presumed to be largely person- or demographic-based [34]. Likewise the link between end-of-life and acute utilization (and hence bed occupancy), has also been not considered to directly influence costs [49], and is only indirectly inferred via the role of age. The highly granular nature of these outbreaks are therefore of profound significance to understanding why the health economy in different locations suddenly appears to tip into deficit [3,67-69], and why associated medical bed occupancy in the local acute hospital also shows a step-change [1,4,6,8,10,62-65]. Indeed it would appear that if governments are serious about restraining increasing health care costs, then research into these outbreaks is an international priority. There are equally profound implications to how we understand the nature of medical conditions and acute medical admissions arising out of these outbreaks.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not required. This study uses publically available aggregate data.

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