

## ORIGINAL ARTICLE

## A Recurring Series of Infectious-like Events Leading to Excess Deaths, Emergency Department Attendances, and Medical Admissions in Scotland

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## ABSTRACT

A series of infectious-like events are characterised within the geographical area of the Scottish NHS Health Boards. Each event leads to a relatively sudden 3% increase in total deaths (around 3,500 extra deaths for Scotland) which lasts for around two to three years. The onset and shape of the time trend is slightly different in each Health Board area and it is this which suggests an infectious spread. There is a general north to south movement in each outbreak with initiation always occurring in Scotland before England. The number of medical admissions and emergency department attendances also rise at roughly the same time as the onset of these events. A similar phenomena has been documented in Australia, Canada and the USA and the effects appear to extend to general practitioner (GP) referrals, occupied beds in hospitals, the trajectory of incidence for specific cancers and a cycle in the gender ratio at birth. The possibility that the ubiquitous immune modifying herpes virus, cytomegalovirus, may be involved in these events is discussed. *Biomed. Int.* 2013; 4: 72-86. ©2013 Biomedicine International, Inc.

**Key words:** cytomegalovirus, emergency department, immunity, infection

## INTRODUCTION

Unexpected increases in medical emergency admissions to hospital have been an enduring feature of all Western health care systems since the early 1990's and perhaps even earlier.<sup>1-8</sup> Analysis of a period of rapid growth in the early to mid-1990's in the UK, Australia and New Zealand led to the general conclusion that the processes of care coupled with increasing expectation of health care and breakdown of the family unit were likely contributory factors.<sup>1-8</sup> However, recent re-analysis of the trends suggests that the increase occurs in rapid spurts of growth which repeat at an interval of between three to nine years, most commonly five to six years, rather than a continuous trend.<sup>9</sup> The increase appears to be largely confined to medical admissions, as opposed to surgical or trauma<sup>9,10</sup>, is confined to a set of diagnoses which would arise out of immune dysfunction, i.e. an increase in particular infections and inflammatory-based conditions<sup>11,12</sup>, has a greater effect against females<sup>13</sup>, has greatest effect against those aged over 60<sup>14,15</sup> and appears to be international in scope, i.e. Australia, Canada, USA and all parts of the United Kingdom.<sup>16-18</sup>

Even more telling is the fact that local step-like increases in medical admissions appears to show a spatio-temporal spread which is also reflected in increased general practitioner (GP) referral for particular conditions and specialties, increased emergency department

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attendances, an increase in excess to expected deaths<sup>14,15,19-22</sup>, step-like increases in occupied hospital beds<sup>23-25</sup>, creates profound increases in particular health care costs<sup>19,26,27</sup> and leads to high uncertainty in forecasts of future activity and costs.<sup>26-30</sup> Across the UK a minimum estimate of 20,000 to 30,000 excess deaths have been attributed to each event/outbreak.<sup>20</sup>

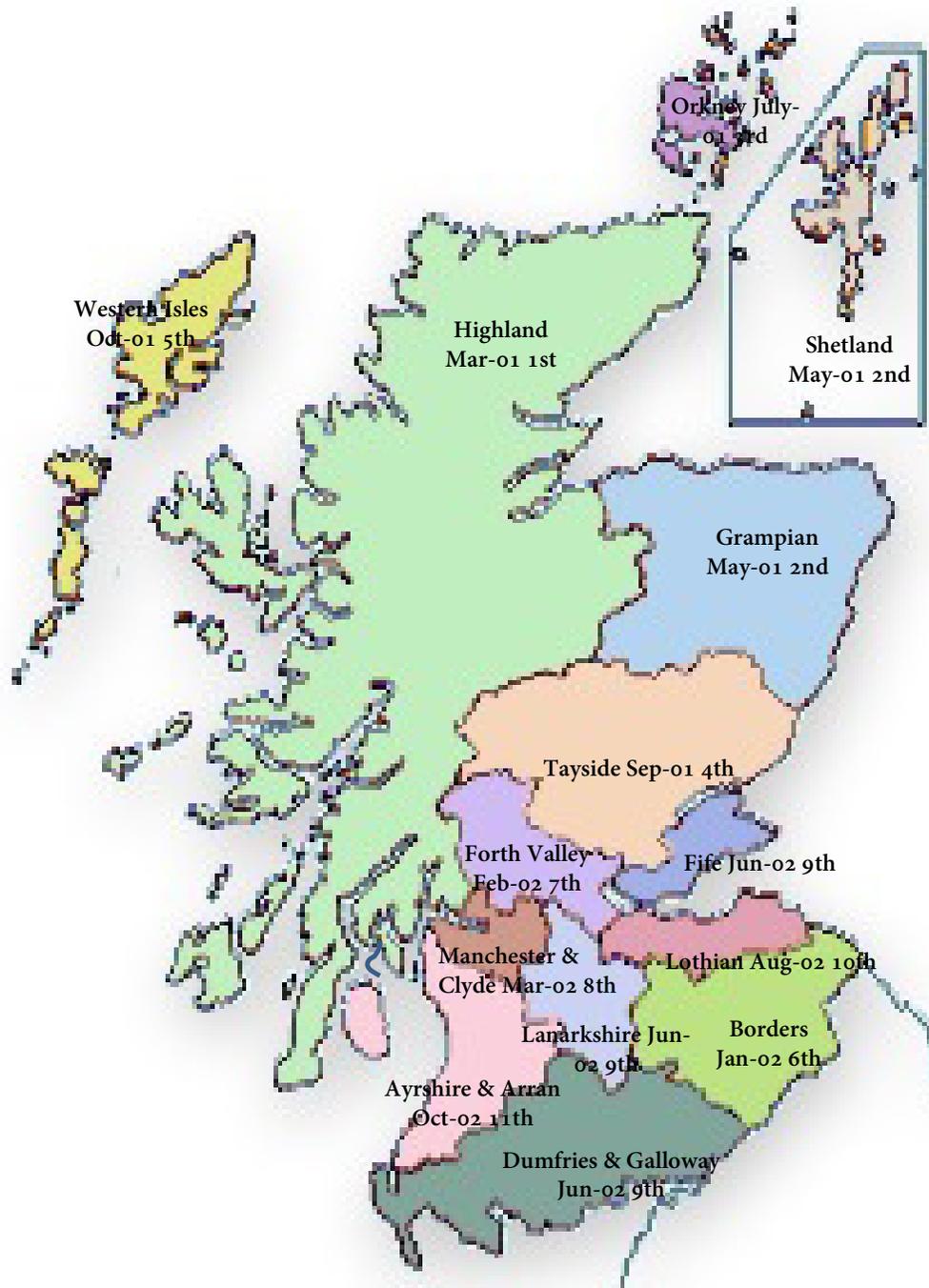


Figure 1: Scottish NHS Area Health Boards and order of the 2001/2002 outbreak.

### Aims

This paper will examine the monthly trend in deaths from January 1990 to December 2012 using Scottish National Health Service (NHS) Board (HB) geographies as the spatial units (see Figure 1). In Scotland fourteen regional HBs are responsible for maintaining their

population’s health and for the delivery of frontline healthcare services. In addition, daily medical admissions are analysed, both in Scotland and England, following the 2007 infectious-like event.<sup>20-22</sup> In this paper these infectious-like events will be referred to as ‘outbreaks’. Monthly trends in emergency department attendance during the most recent outbreak for Scottish HBs are also analysed during 2011 and 2012. The aim of this analysis is to demonstrate that the different measures of mortality and morbidity appear to be following a common pattern which is suggestive of a new type of infectious outbreak.

*Methods*

Monthly data covering deaths<sup>31</sup> and annual deaths by age were obtained from the General Registrar Office for Scotland from January 1990 to December 2012. Due to the fact that deaths show seasonal behaviour the analysis was performed using a running 12 month sum. This removes the bulk of the underlying seasonal behaviour and leaves a time series of 12 month totals which increment forward by one month at a time. In a running 12 month sum a sudden step-like increase leads to a ramp-like feature in the trend. For example, a jump from 100 to 120 deaths per month would commence at a 12 month total of 1,200 (100 x 12). At the first month after the step-change the total would be 1,220 (100 x 11 + 120). After 12 months the full extent of the step-change would emerge and the trend would then plateau at 1,440 (12 x 120) and stay at this level until another change occurred.

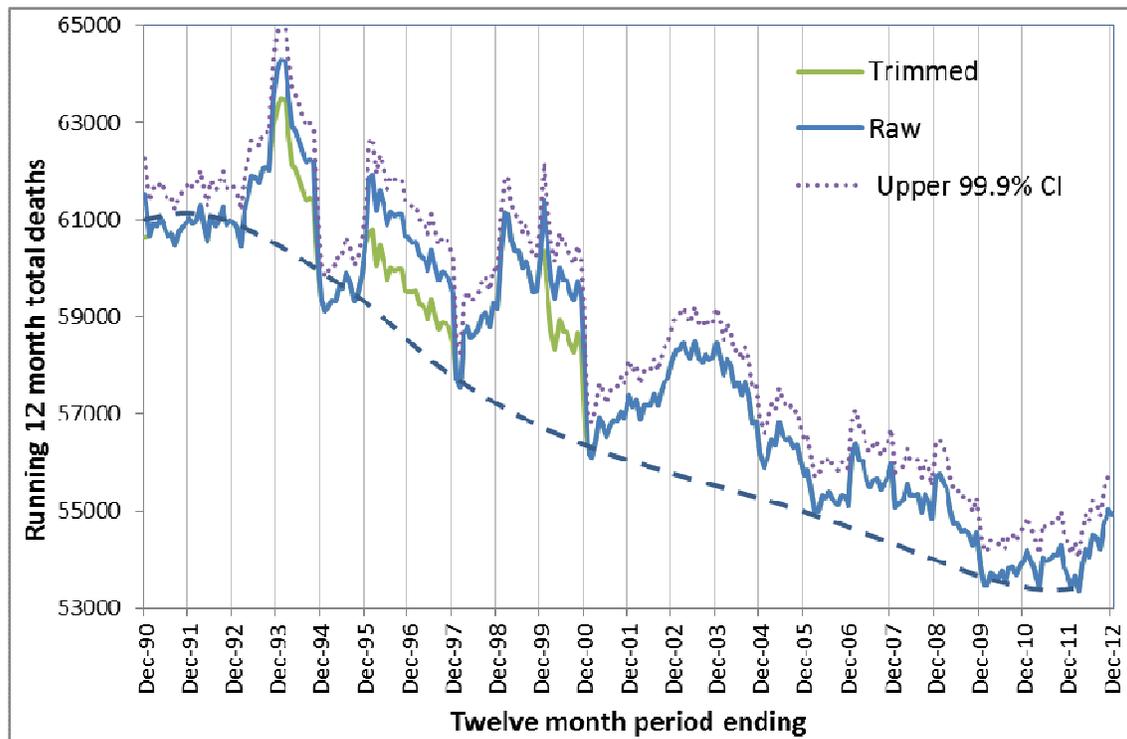


Figure 2: Twelve month running sum for deaths in Scotland.

On the other hand, a single month with a very high number of deaths, say an influenza epidemic, creates an immediate plateau which lasts for 12 months and then returns back to the base-line. Hence a one-off event creates a temporary plateau with sharp sides while a genuine step-increase creates a 12 month long ramp followed by a longer plateau. The running 12 month sum also has the advantage of considerably reducing the statistical variation associated with the smaller monthly totals. Given that the standard deviation of a

Poisson distribution is equal to the square root of the average we can calculate that the 12 month sum will have a standard deviation and hence confidence intervals which are 3.5-times smaller than the monthly data.

Daily emergency admissions to a medical group of specialties were provided by the Information Services Division (ISD) Scotland and the Royal Berkshire Hospital, Reading, England. This data was analysed using the method of CUSUMS.<sup>32</sup> In this method a step-increase creates a ramp whose slope is equal to the magnitude of the step change. Monthly emergency department (ED) attendances were obtained from ISD Scotland.<sup>33</sup>

## RESULTS

*Figure 2* demonstrates six events or outbreaks which meet the criterion of a step-like change followed by a period of higher deaths which lasts for around two to three years followed by a return to the baseline position, which in this case is trending downward due to an increase in life expectancy over the time period. *Figure 2* includes an approximation to the 99.9% confidence interval (CI) to demonstrate that the events cannot be attributed to statistical variation, i.e. the shifts are far greater in magnitude than the 99.9% CI. This approximate CI relies on the fact that the standard deviation of a Poisson distribution is equal to the square root of the average. While the expected average deaths is not known in *Figure 2* the square root attenuates the effect of uncertainty in the average and hence an approximation to the 99.9% CI can be calculated using the actual number of deaths as a proxy to the (unknown) average. Indeed Poisson variation would not operate consistently in one direction for such extended periods of time. However, Poisson variation does place an effective limit on the size of the geographic areas since below around 1,000 deaths it becomes increasingly difficult to disentangle the specific effect of a particular event, i.e. infectious outbreak, from the background variation or noise.<sup>29</sup> Hence at an average of 1,000 deaths for a twelve month sum the standard deviation is, by definition  $\pm 3.3\%$  which is around the size of the step change in deaths (see below) and hence the signal (a step increase in deaths) can become lost or distorted in the Poisson statistical noise.

For Scotland the magnitude of the initial step increase was as follows: Jan-93 (2.5%), Nov-95 (2.5% after adjusting for influenza outbreaks), Mar-98 (2.8%), Mar-02 (2.8%) and Jan-07 (2.9%). In contrast to these step-like events, several years had unusually high deaths (spike events) in January or February (Jan-90, Jan-96, Jan-97, Jan-00, Feb-00) and trimming these spikes back to 6,000 deaths (the general maximum at this time of the year) only had a moderate effect on the overall trend (see *Figure 2*) for particular years, mainly before the year 2000 when influenza activity was higher. This trimming process may overstate the required correction especially for the Nov-95 event since it has been proposed that influenza outbreaks may be potentiated if they occur subsequent to one of the proposed outbreaks.<sup>29</sup> The dashed line, which is a freehand trend, has been added to *Figure 2* to allow visualisation of the periods of extra deaths against a background of declining deaths due to increasing life expectancy. The area under the actual trend and the dashed line gives the total excess deaths which is around 3,500 for most outbreaks.

*Figures 3 to 5* explore the possibility of an infectious-like spread by showing the results for the six largest Health Board areas. Health Boards have been paired based on decreasing size, i.e. number of deaths, where the five events can also be seen but with slightly different shaped responses, including variation in maximum amplitude relative to the baseline, and

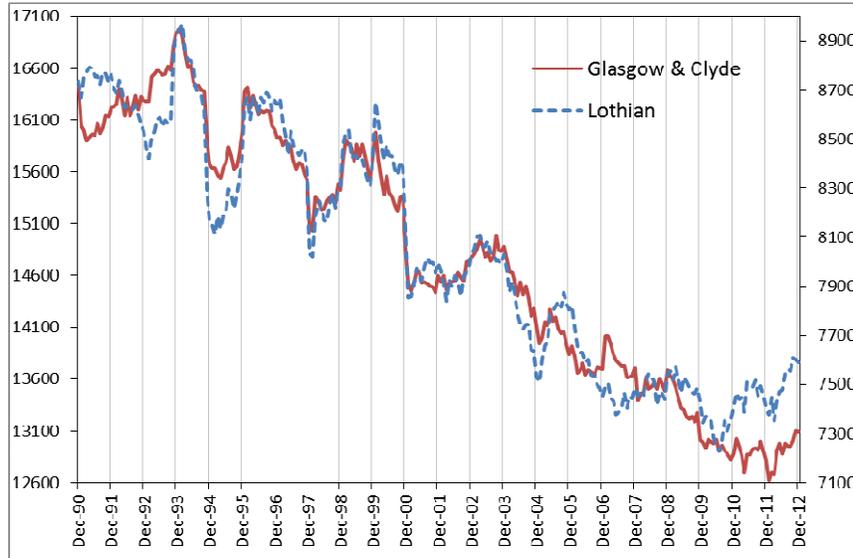


Figure 3: Twelve month running sum of deaths in Glasgow and Lothian Glasgow & Clyde left hand Y-axis and Lothian right hand Y-axis.

differences in timing of the onset. For example, in Figure 3 Lothian generally shows a slightly later start than Glasgow and in Figure 4 Grampian and Lanarkshire show a particularly strong response to the 2007 outbreak. Annual deaths range from around 13,000 in Glasgow and Clyde down to 210 in the Shetland Island. All other Health Boards (not shown) show this variable behaviour which becomes increasingly obscured by statistical variation as the Health Board size reduces.

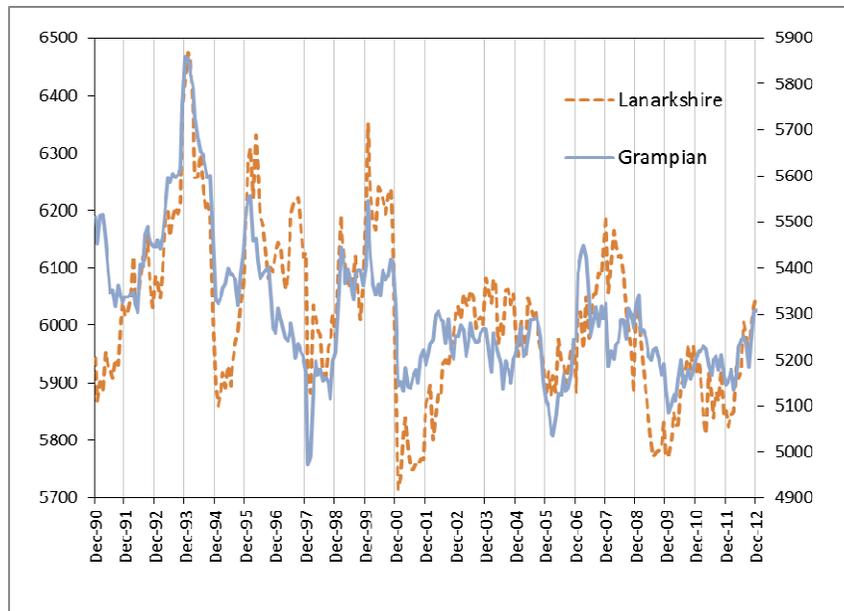


Figure 4: Twelve month running sum of deaths in Lanarkshire and Grampian Lanarkshire left hand Y-axis and Grampian right hand Y-axis.

Figure 6 explores the possibility of wider spread by comparing the timing of the onset of the 2007 outbreak in Scotland with that seen the Royal Berkshire hospital in Reading, England (around 530 km south of Scotland). This hospital has been chosen because it is one of the few hospitals in England where there is a continuous record of inpatient data, along with the step changes in medical admissions that occur when deaths increase<sup>14</sup> and which

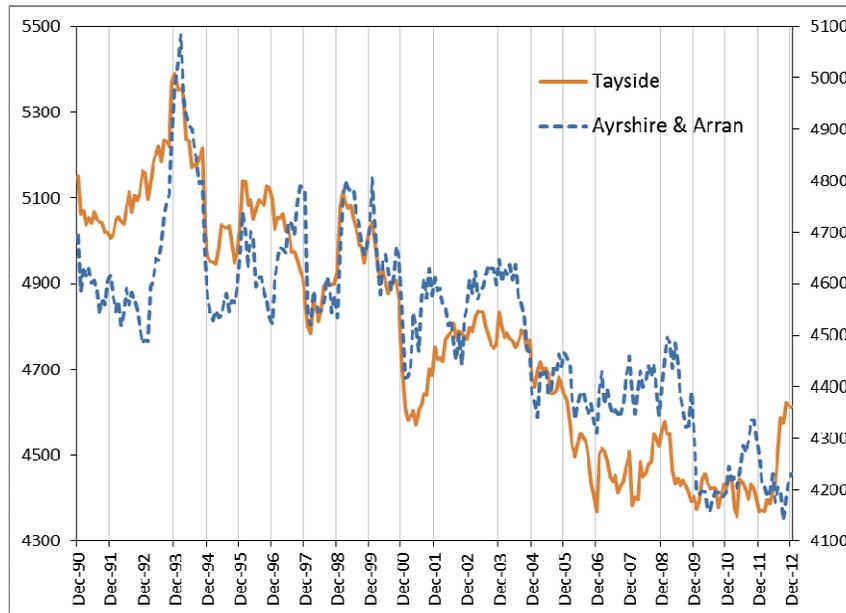


Figure 5: Twelve month running sum of deaths in Tayside and Ayrshire  
Tayside left hand Y-axis and Ayrshire & Arran right hand Y-axis.

matches the time period used for Scotland. On both occasions data is for daily admissions to a medical group of specialties. This chart uses a method called the cumulative sum of differences (CUSUM) as an alternative method to detect the point of onset. The CUSUM method has the disadvantage that seasonal trends are still present and in this respect the seasonal patterns in Scotland and Reading can be seen to be different in that Scotland reached the point of minimum medical admissions earlier in 2006 than Reading. However, this chart is useful because it demonstrates that the point of onset, i.e. the foot of the ramp (marked by the two arrows), can be identified almost to the week and shows the time lag in spatio-temporal spread from Scotland to Berkshire. The subtle differences in the shape of the ramp reflect the speed and extent of the spread across the two respective geographic areas, i.e. across the whole of Scotland versus spread across the catchment area of a single hospital in Reading. However using the entire data series for emergency medical admissions in Reading<sup>14</sup> it is possible to confirm earlier dates for Scotland (based on deaths) on all occasions, namely (Scotland versus Reading), Feb-93 versus Mar-93, Oct-95 versus Dec-96, Oct-98 versus no outbreak, Aug-02 versus Jan-03, Dec-06 versus Nov-07. The absence of the 1998 outbreak in the southern parts of England has been previously noted and it appears to have been confined to just the northern parts nearest to Scotland.<sup>16</sup>

The concept of a spatio-temporal spread is further explored in *Table 1* and *Figure 1* where the point of onset of the major increase in deaths associated with the 2001/2002 outbreak (as an illustrative example) has been calculated for each Area Health Board (AHB). This point was identified by locating the maximum number of deaths in the twelve month running sum and then moving back 12 months, i.e. to the start of the ramp created by using a running twelve month sum. This was then visually checked to see if this point corresponded to the start of the ramp up, recall that a ramp in a twelve month running sum indicates a step-increase in deaths commencing at the foot of the ramp. As can be seen the increase in deaths shows spatio-temporal behaviour. Relatively slow spread tends to eliminate typical respiratory viruses such as rhinovirus (common cold), influenza, SARS, etc., which in any case have only a temporary or spike effect.

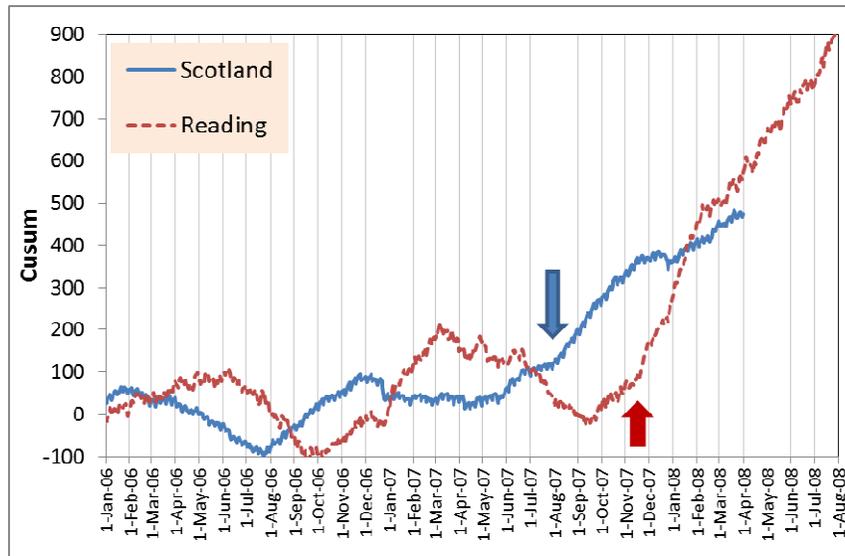


Figure 6: Medical hospital admissions in Scotland and Reading (England) following the 2007 outbreak.

The cumulative sum of differences (CUSUM) for Scotland has been scaled down to match that of the Royal Berkshire Hospital in Reading, England. This was achieved by multiplying Scottish admissions by 0.162 and then subtracting 32.5 (the average daily emergency admissions in Reading during the 2006 calendar year) from both data sets to calculate the daily difference to the 2006 average which is then summed over time to give the CUSUM. The two arrows mark the point where a step-increase in medical admissions commences. Medical admissions comprise an admission to any of the medical specialties, which will include short-stay (acute) general and elderly medicine, cardiology, respiratory medicine, rheumatology, etc. General and elderly medicine accounts for the bulk of the medical group admissions.

Given the past sequence of these outbreaks another outbreak was due to occur at some point between 2012 and 2015. At the time this analysis was conducted data was only available up to December 2012 the initiation and spread of the 2011/2012 outbreak can be discerned at the following points: Fife (May-11), Borders, Dumfries & Galloway (Oct-11), Grampian, Lanarkshire (Nov-11), Western Isles, Forth Valley (Jan-12), Glasgow & Clyde, Lothian (Mar-12), Tayside (Jun-12) Ayrshire (Sep-12). The other regions appearing to have a later start date. The movement of this outbreak beyond Scotland has been confirmed using weekly data from England and Wales where deaths shift to a consistently high state, i.e. higher than the previous three years, from week 15 of 2012 onward, i.e. somewhere around the second week of April 2012. Deaths then continue at this elevated level for the rest of 2012 and into 2013 through to around June.<sup>34</sup>

Figure 7 explores the link between the more recent outbreak and emergency department (ED) attendances. While emergency department attendance is more complex than a simple link to persons whose health has deteriorated to the point that death is immanent it can be seen that a running twelve month total of attendance shows the typical point of onset for a step-like increase that coincides with the onset of increase in death. An increase in ED attendances in England has also been shown to coincide with the point of increased deaths although the effect is greatest for those ED attendances which result in an admission.<sup>35</sup>

## DISCUSSION

In seeking to attribute a cause to these events it should be noted that extremes in temperature are usually only of a short duration, i.e. spike events, and do not lead to large step-changes in the number of deaths.<sup>36</sup> A further possibility is some form of cohort effect. In this respect the World War I and II baby booms are the only cohorts large enough to have a material effect, however, these are 27 years apart, i.e. do not correspond to the periodicity

observed here, and cannot account for the national and international spatial spread. Given the unique population structure in Australia arising from continuous inward immigration since WW II this is particularly relevant to the 2007 outbreak where both deaths (unpublished) and medical admissions show the characteristic step-like increase<sup>18,37</sup>, i.e. we can likewise discount demographic-based explanations. Since around 50% of deaths occur in hospital<sup>29</sup> the final suggestion has been that after any period of higher deaths the number of older people would accumulate which then creates another wave of deaths. This suggestion does not however explain the spatial and international spread of both deaths and emergency admissions.

*Table 1: Initiation and spread of the 2001/2002 outbreak*

Health Board	Onset	Comments
Highland (6.1%)	March 2001(?)	Shape indicates gradual spread (perhaps from Mar-01). Largest AHB in terms of geographic area. Inverness is the largest city but numerous smaller towns.
Grampian (9.7%)	May 2001	Rapid spread indicated by a clear profile over time. Major population locus is the City of Aberdeen (3 <sup>rd</sup> largest in Scotland).
Shetland Island (0.4%)	May 2001 (?)	Only 220 deaths per annum makes precise analysis difficult.
Orkney Island (0.4%)	July 2001 (?)	Only 210 deaths per annum makes precise analysis difficult.
Tayside (8.4%)	September 2001	Rapid spread indicated by a clear profile over time. Contains major population loci in Perth, Kinross and Dundee (4 <sup>th</sup> largest city).
Western Isles (0.4%)	October 2001 (?)	Only 210 deaths per annum makes precise analysis difficult.
Borders (2.3%)	January 2002	Rapid spread indicated by a clear profile over time.
Forth Valley (5.4%)	February 2002	Rapid spread indicated by a clear profile over time.
Glasgow & Clyde (23.8%), Scotland	March 2002	Overall shape for Scotland is driven by the major population locus with 24% of deaths in Glasgow & Clyde AHB. Glasgow is the largest city.
Dumfries & Galloway (3.3%); Fife (7%); Lanarkshire (11%)	June 2002	Rapid spread indicated by a clear profile over time. Major population locus in Lanarkshire is around Wishaw.
Lothian (13.8%)	August 2002	Possibly an earlier and smaller loci with major one commencing Aug-02. Major population centre is Edinburgh (2 <sup>nd</sup> largest city).
Ayrshire & Arran (7.7%)	October 2002	Possibly an earlier and smaller loci but major one commences Oct-02. Major population is around Ayr.

Proportion of total deaths in Scotland for the twelve months ending December 2012 for each AHB is given in brackets.

Both raw and trimmed results have been shown in *Figure 2* simply to illustrate that attempting to remove the incremental effect of influenza epidemics, which were present prior to 2000 and only returned with the 2009 swine flu epidemic (which itself only had a negligible effect on the trends), does not make a material change to the characteristic shape of the trend in deaths.

It has also been suggested that the use of age standardisation may have been a desirable extension of this work. However, age standardisation has not been employed for several reasons.<sup>38</sup> Population forecasts are themselves subject to error (the denominator is uncertain), the rate per age band changes over time (the constant risk fallacy), and the use of age bands assumes that the rate per age band is known with certainty and therefore does not unduly weight particular age bands and that there is a constant profile within each age band which is not subject to scaling error.

Regarding this latter issue the author has observed that both emergency admissions and deaths associated with each outbreak show single year age-specific profiles which appear indicative of ‘antigenic original sin’<sup>39,40</sup>, i.e. the process whereby the immune system is primed to mount an immune defence against the antigen in the family of similar antigens (say different influenza strains) to which the individual is first exposed. This creates cohorts of individuals all exposed for the first time to a particular antigen in a particular year whose immune response may then be ineffectual against a later strain of the same infectious agent. Antigenic original sin creates typical saw tooth age patterns<sup>40</sup> which present a

considerable (and often unacknowledged) challenge to age standardisation since the age patterns do not follow the typical five year age bands used in age standardisation but depend on the duration between outbreaks with different strains of the agent. In any case population age structure cannot change in the space of a few months at the rate implied in these studies and the raw trend in total deaths, emergency admissions or emergency department attendances per se, rather than age adjusted, has therefore been used. Furthermore this gives powerful testament to the impact of these outbreaks on the health service in that admissions, attendances and costs suddenly and unexpectedly increase in a sustained manner.

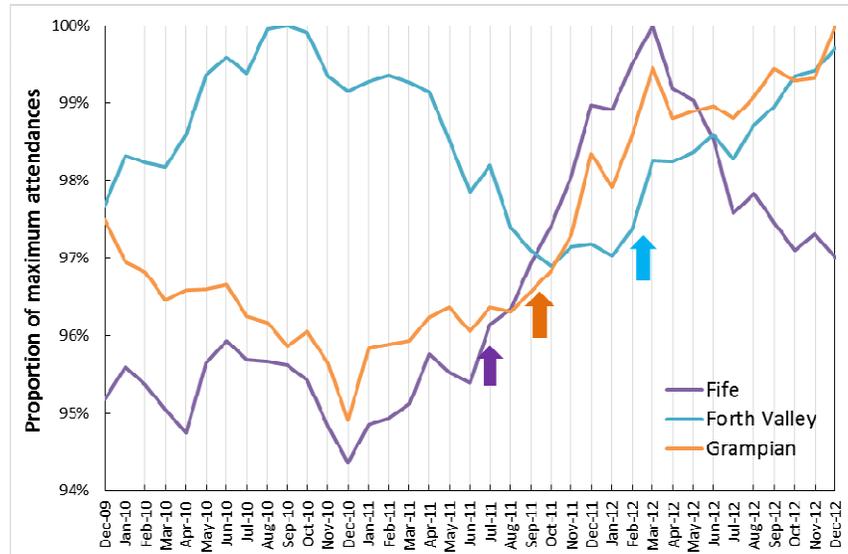


Figure 7: Twelve-month running sum of emergency department attendance.

The arrows indicate the points at which deaths increase in each HB, first in Fife then Grampian and then in Forth Valley. Since the number of emergency department attendances is different in each location the attendance data for each location was scaled by dividing the 12 month running sum by the maximum 12 month total for each location.

The ability of infectious outbreaks to cause such a rapid increase in deaths is well recognised, although most outbreaks do not lead to a sustained increase in deaths. However an outbreak of a persistent infectious agent (such as any of the herpes viruses, etc.) would lead to such a sustained increase especially if the main target were the elderly – as will be the case with deaths. In this respect in 2008, 50% of deaths in Scotland occurred at an age above 75 years (age 70 in males, 77 in females) and the more recent 2012 outbreak in England resulted in increased mortality especially in those over 85 years.<sup>34</sup>

A repeating series of infectious outbreaks is a characteristic of all infections where there is an element of acquired immunity and the period between outbreaks is a unique characteristic of different infectious agents which depend on the interplay between levels in the host reservoir, environmental factors, natural immunity and immunisation.<sup>41,42</sup> The high level of granularity associated with each event is consistent with the behaviour of an infectious outbreak<sup>43-45</sup> where spread occurs as a series of random events and person to person contacts.<sup>46</sup> On this occasion the speed of the spread is relatively slow and this suggests direct person to person contact. There is no population demographic-based phenomena which could explain the series of events or the apparent spatio-temporal spread which extends beyond the boundary of Scotland to the whole of the UK and other Western countries.<sup>9,16-19,27</sup>

Given the significant contribution of each outbreak to the trend in deaths a dashed line was added to *Figure 1* to provide some idea of the potential underlying trajectory in the absence of the outbreaks. The curious minima in deaths before each outbreak also appears to be reflected in a minima in emergency medical admissions, emergency department attendances and total costs.<sup>16</sup> This suggests that in the absence of an ensuing outbreak both deaths and emergency medical admissions could drop even further, i.e. to what extent are these outbreaks defining the trends in death, medical admissions and wider costs?

The suggestion of a general north to south spread within the UK has been previously noted both for the 1993 and 2007 outbreaks<sup>19,47</sup> and in this respect it would be of interest to study the corresponding changes in deaths for regions within Norway, Sweden and Finland to see if the ultimate point of origin is further north than Scotland. The authors own unpublished research regarding the 2007 outbreak suggests that similar changes occur for deaths in Australia (southern hemisphere but high volume air travel with the UK) but with major onset around June 2007. This later onset than Scotland tends to suggest a time cascade in the wider spread.

Spread across Scotland and elsewhere may not necessarily follow an exact geographic pattern but will depend on initiation (a new strain?) and subsequent spread. These will depend on random contacts within social and business travel patterns. Indeed the pattern of spread for the 2001/2002 and 2011/12 outbreaks discussed here are different as is the pattern for the 2007/2008 outbreak demonstrated using the increase in GP referrals across Scotland, England and Wales.<sup>14</sup> It is entirely possible that emergency departments, hospital wards and nursing homes may well act as points of further infectious spread.<sup>48-51</sup>

Wider spread across the whole of the UK has been confirmed both with respect to deaths and hospital medical admissions<sup>9,20,29</sup>, as opposed to surgical or trauma admissions which do not appear to be affected. A time cascade for GP referrals has also been observed and within this cascade there appear to be additional time lags particular to different conditions.<sup>21,22,52</sup> These time lags suggest that the effect of the infection is progressive in nature with some conditions having more immediate effects while others require a longer period before clinical manifestation. Preliminary evidence for the 2012 outbreak in England suggests that there is also an age cascade with initial high deaths for those aged over 85 during 2012 followed by higher deaths in the age groups under 85 during 2013 (unpublished analysis).

The issue of time lags is relevant when it comes to attempts to correlate admissions and deaths, etc. It is known that in the elderly the admission rate starts to increase around 10 weeks prior to death and markedly so at 5 weeks prior to death rising to a maximum near to death.<sup>53</sup> It would be natural to expect that ED attendance and emergency admissions should be a leading indicator while deaths may be a lagging indicator. Indeed this appears to be the case in *Figure 7* where ED attendance appears to increase approximately one month before that for deaths. Pulling various strands of evidence together suggests that spread may be faster in areas with older people, more females and with higher population density.

Cytomegalovirus, a ubiquitous herpes virus with powerful immune modulating effects, has been proposed as a potential cause of these outbreaks, especially in the elderly, via an effect against immune function and this has been the subject of recent reviews.<sup>54-57</sup> The key features are increasing CMV sero-prevalence with age, general effects against infection and

inflammation and specific effects against those who react to CMV infection in a pro-inflammatory way. Hence in one study of geriatric inpatients some 39% had an active CMV infection compared to 13% in the control group<sup>58</sup> while in another study T cell responses were more intense in elderly subjects aged 85 and above who were in poor health and were inversely correlated with markers of functional activity and cognitive function.<sup>59</sup> A cohort study (1992-2002 which encompassed three or four outbreaks) of 635 community-dwelling women, aged 70-79 years demonstrated that women in the highest quartile of CMV antibody concentration had a greater incidence of frailty (hazard ratio = 3.5, 95% CI: 1.5-8.3) and mortality (hazard ratio = 3.8, 95% CI: 1.6-8.8). CMV antibody concentration in the highest quartile independently increased the risk of 5-year mortality (hazard ratio = 2.8, 95% CI: 1.2-6.4).<sup>60</sup> Finally a study investigating 290 hospital admissions for severe CMV infection in immunocompetent adults revealed a 6% mortality rate, although higher in those aged 55+ years and in patients with diseases affecting the immune response (diabetes, renal failure, pregnancy and non-haematological malignancy). Of greatest interest was the fact that the range of conditions associated with the infection was surprisingly diverse including colitis, various central nervous system conditions, haematological disorders, vascular thrombosis and pneumonitis.<sup>61</sup>

With respect to the specific effects of CMV leading to death another study of mortality among elderly Latinos showed that those with CMV seropositive status had 1.43-times higher all-cause mortality over the nine year period 1998 to 2008<sup>62</sup>, which encompasses three possible outbreaks of the proposed agent. A further study which utilised a US nationality representative population over a time period encompassing two or three outbreaks demonstrated that CMV seropositive was associated with a 19% increase in all-cause mortality which rose to around +30% for all-cause and cardiovascular-related mortality in individuals with high levels of C-reactive protein (CRP) which is an indicator of an inflammatory response.<sup>63</sup> The EPIC-Norfolk (England) study which ran from 1993 to 2011 (spanning four outbreaks) demonstrated that CMV infection was associated with a 16% increase in all-cause mortality (6% for cardiovascular disease, 13% for cancer and 23% for other causes) with mortality increasing with levels of immunoglobulin G (IgG) such that all-cause mortality had a 26% increase in the high IgG group.<sup>64</sup> A further study conducted in England and restricted to those aged 65+ over an 18 year period demonstrated that CMV seropositive was associated with a 42% increase in mortality largely due to a near doubling in cardiovascular disease related deaths but with no apparent increase from other causes.<sup>65</sup> Finally a study of hospital diagnosis prior to death following the 2007 outbreak in England has identified a potential match between diagnoses showing an increase and the spectrum of known cases of CMV induced death.<sup>20</sup>

Hence it would appear that CMV is more than capable of accounting for the increased deaths observed in this study and for the associated increase in hospitalization. It is also of note that the trajectory of incidence of specific cancers which appear to change at each outbreak look to involve cancers where CMV has been demonstrated to be either directly oncogenic or oncomodulatory.<sup>28</sup> In England and Wales the timing of these outbreaks also coincides with a temporary increase in the gender ratio (male:female) at birth which is then followed by a decline in the gender ratio that continues through to the next outbreak.<sup>66</sup> A relatively slow spread also matches with the known mode of person to person transmission for CMV via body fluids.<sup>67,68</sup> At this point it is of interest to note that the apparent absence of full spread across the UK for the 1998/1999 outbreak is mirrored in the data for gender ratio at birth<sup>66</sup> in England and Wales. This is probably an important obser-

vation and could suggest that a particular combination of weather or environmental conditions may have intervened to prevent further spread. Further study is required.

Analysis of trends in hospital occupied beds per death (all-cause mortality) over the last decade in both Australia and England has shown that the ratio of occupied beds per death has remained relatively constant.<sup>69</sup> This is due to the fact that the bulk of a person's lifetime bed occupancy (and admissions) occurs in the last year of life, i.e. proximity to decease rather than age *per se* is the key factor. For this reason the downward trend in deaths from 1990, which is more pronounced in Glasgow and Lothian (*Figure 3*), creates a confounding trend for the correct analysis of emergency admissions. Since the trend downward in deaths has levelled off by around 2008 the analysis of emergency admissions in *Figure 6* was confined to the last outbreak where it is easier to see the direct linkage. It should be noted that the shape of the trend in medical admissions for Scotland covers a wide geography while that for Reading is mainly for admissions from within an 18 km area surrounding the Royal Berkshire hospital and will therefore reflect local conditions for spread. As was demonstrated all other outbreaks initiated earlier in Scotland than in Reading.

A feature of note is the apparent change in the shape of the time trend for each outbreak from before 2000 to after. One possible cause is the fact that early in 2000 influenza activity declined to a 100 year minimum, an event which had only occurred previously between 1879 to 1889.<sup>70</sup> Based on analysis of the 1996 outbreak in England this author concluded that there may be some degree of additive or synergistic interaction between the two infectious agents especially when the proposed outbreak occurs prior to an influenza outbreak.<sup>29</sup> In this respect recent research has shown that those aged 65+ with the highest CMV antibody titre have over a 4-times lower response to influenza vaccination<sup>71</sup> indicating impaired ability to withstand an influenza epidemic and other research indicates that CMV induced immune changes in the elderly may be responsible for delayed clearance of the influenza virus from the lung.<sup>55</sup>

## CONCLUSIONS

Evidence has been presented for a type of infectious-like outbreak which appears to involve a persistent infection (presumably viral) which creates profound disturbances in aspects of health care arising out of immune dysfunction, especially in the elderly, leading to adverse health outcomes (hospitalisation and death) and wider increased costs. Regarding the latter the author has estimated an incremental cost of £6billion for the NHS in England following each outbreak and it is this which appears to contribute to the observed cycle of surplus and deficit seen in the UK and elsewhere.<sup>17,25,27</sup> The variable impact on deaths demonstrated in different parts of Scotland (*Figures 3 to 5*) points to the variable impact upon costs<sup>29</sup> and hence the difficulty of assessing the true level of funding required for different locations.<sup>27-29,72</sup> Subsequent spread of the 2011/2012 outbreak into England has recently been confirmed with onset of increased deaths and emergency admissions commencing in February 2012 along with very high levels of granularity between smaller local authority geographies.<sup>34</sup>

Urgent research is required to confirm the identity of the infectious agent; i.e. is CMV the direct cause or is it merely re-activating en mass in response to another agent, and further quantify the profound effects upon health and health care costs. Alternately, if we are not dealing with an infectious outbreak then a coherent hypothesis needs to be formulated to explain the common pattern which is observed in deaths, emergency medical admis-

sions for specific conditions, GP referral, emergency department attendances, the gender ratio at birth and changes in the incidence of particular cancers.<sup>9-30,34,35</sup> The presence of these unique infectious outbreaks will also have implications to the formulation of the statistical algorithms for detecting different types of infectious outbreaks and automated mortality monitoring.<sup>73</sup>

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