



# Unexpected and Disruptive Changes in Admissions Associated with an Infectious-like Event Experienced at a Hospital in Berkshire, England around May of 2012

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## Author's contribution

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

## Article Information

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## ABSTRACT

**Aims:** To study the effect of a large infectious-like event on admissions to, and bed occupancy in, a very large acute hospital in Reading (western Berkshire) England, observed to commence in the early part of 2012. These changes occurred in parallel with infectious-like spread of an agent leading to increased medical admissions across the whole of Berkshire.

**Study Design:** Longitudinal study of hospital admissions, bed occupancy and deaths.

**Place and Duration of Study:** Admissions and deaths at the Royal Berkshire Hospital NHS Foundation Trust (England) between April 2008 and September 2013.

**Methodology:** A running 12 month total of admissions, deaths and occupied beds was constructed from aggregated hospital admission and discharge data. Trends were analysed by admission type, discharge destination, specialty, International Classification of Diseases (ICD-10) primary diagnosis and Healthcare Resource Group (HRG) v4 chapter.

**Results:** Admissions, deaths and occupied beds all showed a simultaneous step-like increase around March to June of 2012, which led to considerable operational pressure and a marked reduction in elective overnight surgery due to reduced bed availability. The increase in in-hospital

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deaths exhibited a curious time cascade which was specific for various diagnoses. Deaths first increased for those with cancers or intestinal conditions in January 2012, followed by hepatic, diabetic and asthma in February 2012, then a time series of other conditions, through to arthritis and arthrosis conditions in July 2012. All of these occurred at a time when deaths across the whole of the UK showed a large and unexpected increase.

**Conclusion:** A new type of infectious event is strongly implicated which appears to exert its clinical effects via some form of immune impairment. The agent leads to a persistent infection. The immune modifying virus, cytomegalovirus, which (in other studies) is associated with a 20% higher odds ratio for all-cause mortality, has been circumstantially implicated, however, this requires confirmation.

*Keywords: Emerging infectious diseases; hospital admission; death; diagnosis; cytomegalovirus; immune impairment; bed occupancy; step-like increase.*

## 1. INTRODUCTION

The Royal Berkshire Hospital NHS Foundation Trust (RBH), is a very large acute hospital situated in Reading, West Berkshire, in the south of England. In 2012 this hospital had over 600 adult acute overnight beds, 200 dedicated day beds/bed equivalents, 44 pediatric and 57 maternity beds. Like many hospitals in England, during 2012, it experienced a large and unexpected influx of emergency department (ED) attendances (many of whom were subsequently admitted) and wider medical admissions.

In the UK there is accumulating evidence for large spurts in growth in medical admissions which can be seen in the years 2003, 2008 and 2012, and also in earlier years [1-11]. These correspond to large and unexplained peaks in death [12-14]. The changes occurring in these years also show evidence for age and condition specificity [15]. Hence the peak in deaths in 2012 involved high specificity for those with neurodegenerative diseases [16-17], respiratory conditions [18] and digestive and vascular conditions (in preparation), along with single-year-of-age specificity in deaths and admissions [19]. However, is this really a new phenomenon?

In 1969 the Western Infirmary in Glasgow reported a 27% increase in medical admissions in the six months August 1969 to January 1970 compared to the same period a year earlier [20]. A similar large increase also seems to have occurred in Scotland in late 1984 or early 1985 [21]. A similar surge can be discerned in Scotland and parts of northern England in early 1991 [22]. In the financial year 1993/94 emergency admissions for the whole of England had increased by 7 to 13% compared to 1992/93 [23-25]. At the Aintree hospital in Liverpool there was a 37% increase in medical admissions with

an unexpected large increase in the 15 to 44 age group. In nearby Manchester, admissions to one mental health hospital increased by >30% [25]. Parallel increases in medical and mental health admissions were replicated across the whole of England, and medical admissions at the Royal Berkshire Hospital increased unexpectedly by 13%, via an abrupt increase commencing in the middle of March 1993 [2], as did the number of occupied medical beds [5]. Similar events in 1996 and 1999 led to concern that the increase was unsustainable, and created heated debate regarding causes and solutions [21-30], and prompted numerous studies both in the UK and elsewhere [24,31-35]. Historic events such as these, are usually dismissed as having little relevance to present day changes and pressures in the NHS within the UK.

Another report by the Nuffield Trust suggested that increases in emergency admissions between 2004/05 and 2008/09 were largely due to a reduction in admission thresholds [36]. However, this assumption contradicted the conclusions from other studies. In the first, research in the USA had demonstrated that acute admission thresholds are maintained despite considerable fluctuation in demand [37], while in the others it was suggested that emergency medical admissions rose in sudden spurts [5-7], as per the reports cited above. Indeed, the data presented in the Nuffield Trust report shows evidence for one such spurt of growth at the end of the study period, although the significance of this seemed to have been overlooked within the study, but was noted by others [30].

The sudden increase in emergency department attendances and associated medical admissions in 2012, received much attention and a report on emergency and urgent care was subsequently published by NHS England [38] along with

planning guidance 'Everyone Counts' covering the 2013/14 financial year [39]. Both of these documents imply that the problems are largely to do with the way NHS organizations deliver care and in a lack of integration between health and social care. While there is a strong case for change in the way services are delivered *per se*, it is curious that neither of these two documents raise a possible link between the increased deaths in 2012 and the parallel increase in unscheduled care.

A role for deaths in hospital admissions arises from the fact that a person's lifetime usage of a hospital bed is concentrated in the last year of life, irrespective of the age at death [40]. In this respect it should be noted from Table 1 that the increase in deaths in 2012 in the local authority areas surrounding the Royal Berkshire hospital showed a local hot spot relative to the national average and, by implication, this hospital may have experienced an unusual increase in medical admissions and associated in-hospital deaths.

**Table 1. Increase in deaths (all-cause mortality) in 2012 compared to 2011 in the local authorities surrounding Reading**

Local Authority	Age 60+	Age 80+	± SD
South Oxfordshire	11%	16%	3.0%
Reading	13%	13%	3.3%
Wokingham	10%	11%	2.8%
Bracknell Forest	8%	10%	3.3%
West Berkshire	3%	7%	3.1%
<b>England</b>	<b>4%</b>	<b>6%</b>	<b>0.2%</b>

*Standard deviation (SD) is from Poisson variation for the Age 60+ increase, although this figure roughly applies for both age categories.*

A number of recent studies on the 2003, 2008 and 2012 events have demonstrated infectious-like spread affecting both death, hospital admission and GP referral for an outpatient attendance. The first is a study on the monthly patterns of death in Scotland from 1990 to 2012, where spatial spread in deaths between Scottish Health Boards is clearly evident for a recurring series of these events [1]. Similar conclusions have been reached using smaller local authority areas in Scotland [41]. The next is a series of three studies showing very small area spread leading to large increases in emergency medical admissions in North East Essex following the 2008 event [42], and in Wigan (near Manchester) [43] and Berkshire following the 2012 event [44].

The Berkshire-wide study accompanies this paper in this journal. The increase in GP referrals subsequent to the 2007 event, has likewise been shown to involve time-based spatial spread across the UK [45]. Lastly, the unexpected increase in deaths seen in England and Wales during 2012 has been demonstrated to show single-year-of-age specificity, which would be expected to arise out of the effects upon immunity of a recurring series of infectious events via different strains of the same agent [19]. Analysis of medical admissions following a similar event in 2007 has demonstrated a similar increase in medical admissions in Northern Ireland, Wales, Australia, Canada and the USA [9,46-47].

Clearly this sheds new light on what is happening. Hospitals do not control all-cause mortality and certainly do not control large and small area infectious-like spatial spread in both deaths, medical admissions and GP referral for an outpatient attendance. More intriguingly, both the NHS in England and the Healthcare Insurance Industry in the USA appear to have been subject to a long-term cycle in surplus and deficit, which has endured for many years despite vast differences in policies and health care organization [48-50]. The gender ratio at birth in England also shows a similar long-term cycle [51]. All of these show evidence for a common source. Clearly something out of the ordinary is happening which requires further investigation. These unique happenings have never received an adequate official explanation. Indeed a report by Public Health England into winter deaths in 2012/13 appeared to give the impression that the increased deaths occurring throughout the whole of 2012, was due to a 'bad' winter [12], i.e. the effect of the ongoing outbreak (i.e. higher winter deaths) was substituted as a cause for the whole year increase.

None of the above ignores the fact that there are potentially avoidable and preventable emergency admissions [52-54], nor the fact that certain aspects of acute and primary care lead to higher than average emergency admissions [53-55]. Neither does it suggest that schemes to both anticipate and reduce emergency admissions, especially in the elderly, should not be implemented [56-61]. The above mentioned studies are merely pointing out that something which is out of the ordinary is happening, which leads to rapid spurts of growth in emergency admissions, and that such spurts have been reoccurring for many years. Unfortunately, in the

absence of a knowledge of small-area infectious spread and of a link between deaths and medical admissions, almost all the earlier studies reached a *de facto* conclusion that societal factors coupled with inefficiency in health and social services was the sole source of the overall increase [32-36]. These factors are merely contributory to a long-term rise, but cannot explain the spurts in growth, which display spatial spread, and a link with unexpected peaks in death. Outbreaks of a type of immune modifying agent have been proposed to account for this curious behavior [see reviews 3-4,8-10,16-18], however it is the measurable consequences which are the focus of this study.

Having documented small area spread throughout Berkshire following the 2012 event [44], this study investigates the impact of the presumed infectious outbreak on the Royal Berkshire Hospital in the western part of Berkshire. As was seen in Table 1 this hospital is surrounded by local authority areas which experienced some very large increases in death in 2012 (compared to the national average), through to more moderate increases in the West Berkshire local authority. The small area study (which accompanies this paper), has shown that the lower increase in deaths in 2012 in West Berkshire is due to more pronounced spread of the infectious-like agent in 2013 rather than 2012 [44]. This study will therefore investigate the influx of medical admissions and related trends in deaths associated with particular conditions which occurred at the Royal Berkshire Hospital in early 2012. For each patient admission (Spell), there can be multiple Finished Consultant Episodes (FCE) as the patient passes from the care of one consultant to another, depending on the complexity of the condition. Issues relating to the complexity of admissions will be explored using both FCE- and Spell-based data.

## 2. MATERIALS AND METHODS

### 2.1 Data

Aggregate hospital statistics (avoiding any patient identifiable features) covering admission type, specialty of care, primary diagnosis, Health Resource Group (HRG) code was extracted for analysis over the period 2008 to 2013.

The data used in Table 1 for deaths during 2011 and 2012 in English Local Authorities (LAs) was obtained from the Office for National Statistics (ONS). Monthly data for deaths in LAs

surrounding the hospital were also from the ONS.

### 2.2 Analysis

Time trends were analyzed surrounding the 2012 event using a running annual (365 day or 12 month) sum. Such running totals diminish the contribution from within-year seasonal cycles in admissions, and allow the precise identification of the time at which a large and semi-permanent increase in admissions has occurred [1,41-45]. A running sum starts with the first 12 month period, say Apr-08 to Mar-09, moves forward one month (May-08 to Apr-09), and continues these one month at a time increments over the entire time period. The value of the step-like increase is determined by comparing successive twelve month periods each side of the step-like increase. For example, the 12 month total Jan-11 to Dec-11 is compared with Jan-12 to Dec-12. If the latter is, say, 10% higher, this is the extent of the step-like increase which is then checked for statistical validity (see below).

Monthly occupied beds were calculated from the sum of monthly occupied bed days divided by the number of days in each month [5]. Seasonal adjustment to monthly occupied beds was achieved by minimizing the sum of absolute differences between adjusted month-of-year values using the Excel Solver function. The Solver function simultaneously optimizes all values (the adjustment factor for each month) to achieve the objective (a minimum sum of between month residuals).

Any total from discrete (integer) events will be subject to Poisson variation. By definition the standard deviation of a Poisson average is equal to the square root of that average. The potential contribution from Poisson variation to the value of any step-change, was evaluated using Monte Carlo simulation of the ratio of two Poisson distributions (before/after). The 97.5% confidence Interval (CI) was calculated with 200,000 trials using Oracle Crystal Ball for an annual total (N) of between 100 and 700, in increments of 100. The resulting 7 values were plotted using Microsoft Excel and follow a power function where  $97.5\% \text{ CI} = (1.965 \times N^{-0.0891})^{-1}$ . This equation was then used to calculate the 97.5% CI associated with the step-increase.

### 3. RESULTS

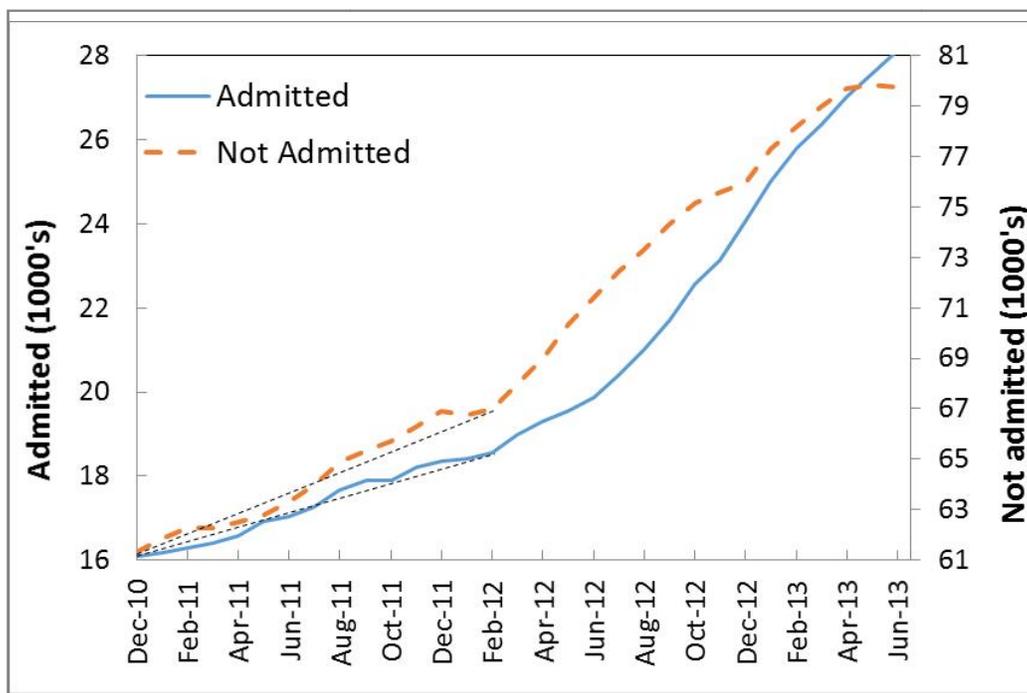
#### 3.1 Trends at the Emergency Department

The trends in attendance at the emergency department (ED) surrounding the 2012 event are presented in Fig. 1, where it can be seen that both admitted and non-admitted attendances increased at a point after February 2012. There was a highly significant increase both in attendances which were discharged (+22.2%), and those resulting in an admission (+25.3%), (after adjusting for the background increase). Note the full extent of the increase in a running 12 month sum chart is 12 months on from the point the slope starts to change and that GPs can admit directly to certain medical beds and to assessment units and these will by-pass the ED. The next section will therefore examine the trends in admissions.

#### 3.2 Trends in Admissions

The running 12 month total employed to detect the onset of the outbreak requires some explanation. As would be expected of an

infectious outbreak the point of onset is not abrupt, however, to maintain consistency of terminology, the point at which the maximum step-like change has occurred has been chosen to approximate the onset. For example, in discharge to another hospital using FCE the increase was +39% in May and +40% in June, while for discharge to a nursing/care home the increase was +62% in April, +67% in May and +65% in June, hence by inference the initiation date is probably accurate to  $\pm 1$  month. The size of the step change is determined from the relative number of admissions in the 12 months preceding the step-like increase, and the 12 month period immediately after, i.e. by definition the step-like change has to endure for twelve or more months, and it is these semi-permanent increases which are a characteristic of these particular outbreaks. Where the outbreak has been said to commence in May, implies that the point of maximum increase occurred toward the end of May or possibly early June, although as with any outbreak, depending on the incubation period and routes of transmission, initial arrival of the agent could be weeks or months earlier.



**Fig. 1. Running 12 month sum for emergency department attendances**

*The two dotted lines show the trend prior to the abrupt change occurring around March 2012 for 'Not Admitted' attendances, and between March and June 2012 for Admitted patients.*

Large, and sudden changes in the source of admission, i.e. where the patient has arrived from, are investigated in Table 2 and are shown to occur mainly around May in 2012. Since the hospital has no direct control over the source of admission the changes are highly suggestive of an event external to the hospital. On this occasion Spell-based data is not available, and the percentage increase noted for certain admission sources may be inflated due to higher proportions of complex patients. Note the associated reduction in elective admissions, which is far worse for overnight admissions, suggests knock-on effects due to bed availability (see Section 3.3). On this occasion elective day case admissions will be unaffected since the 204 dedicated day beds (or bed equivalents), are separate to the overnight stay bed pool. Admissions from 'other hospital' are usually patients transferred to a larger tertiary hospital for specialist surgery/treatment, who are then admitted back for recovery and rehabilitation, hence imply an increase in patient acuity/complexity.

**Table 2. Changes in source of admission (all specialties)**

Source	Initiation	Change
ED/GP (emergency)	May-12	47%
Other hospital*	May-12	132%
Outpatient clinic*	May-12	98%
Post-partum	May-12	11%
Elective admissions	May-12	-4%
Elective overnight	May-12	-13%

*Note that these are FCE-based figures and hence an admission can be counted more than once. Divide the percentage increase associated with FCE by 1.9 to adjust for double counting of FCE per Spell, excludes Maternity where the ratio of FCE: Spell is close to 1.0. See later discussion on the changes in the ratio of FCE per Spell. (\*) Large percentage increases are associated with small numbers of admissions*

Table 3 further explores this issue by looking at changes in discharge destination which further

**Table 3. Changes in discharge destination (all specialty/types)**

Destination	Initiation	FCE	Spell
Hospice	Mar-12	30%	0%
Other Hospital	Jun-12	40%	6%
Nursing/Care Home	May-12	67%	7%
Prison	Apr-12	67%	40%
Psychiatric/Mental Health	Apr-12	96%	44%
Died	May-12	69%	13%
Temporary Residence	Apr-12	116%	40%
Usual Residence/Home	May/Jun-12	11%	7%

*Note that large percentage increases are associated with small number events.*

reinforces the idea that specific groups are affected more than others, and that complexity (the ratio of FCE per Spell) increases for certain patient groups. Note that patients *already* living in a care/nursing home will be admitted and discharged to 'usual place of residence', and patients whose condition has deteriorated to the point of *now requiring* a care/nursing home will be discharged to a care/nursing home as the discharge destination, i.e. there has been a specific increase in those who are now too frail to stay at home.

Table 4 demonstrates that the changes are specialty-specific, with emergency admission to medicine most affected. Medical conditions are admitted to other specialties and this accounts for the increases in ENT, Ophthalmology and Urology admissions (see Table S1 in the supplementary material). Note that emergency Ophthalmology admissions usually range from 86 to 104 per annum and a 99% confidence interval (CI) of around  $\pm 30\%$  will apply due to Poisson variation. In those specialties where there was an increase, the increase endured for a period of 12 to 18 months before beginning to decline, i.e. this is not a short-term infectious spike typical for some conditions such as influenza.

In England, following the 2008 outbreak, the Department of Health took the decision to mitigate the increasing cost of emergency admissions by imposing a 70% discount on the cost of an emergency activity which is higher than the 2009/10 out-turn [62]. Hence there is no financial advantage to be gained by the hospital in increasing emergency admissions, on the contrary the 70% discount (on full cost) leads to a considerable loss on each admission leading to hospital deficits [63]. Hence there is no rational reason for any hospital to voluntarily increase emergency admissions.

**Table 4. Changes in emergency admissions by specialty groups**

Group	Initiation	FCE	Spell	97.5% CI
Head & Neck	Apr-12	29%	26%	11.3%
Maternity	Apr-12	6%	6%	2.5%
Surgical	May-12	14%	0%	3.7%
<b>All Specialties</b>	<b>May-12</b>	<b>30%</b>	<b>7%</b>	<b>1.3%</b>
Medical	May-12	60%	17%	2.0%
Oncology & Haematology	May-12	65%	0%	14.0%
Paediatrics	Jun-12	17%	17%	3.7%

*The ratio of FCE per Spell is closer to 1.0 in some of the surgical group of specialties. In the Surgical group only Urology shows a change of 6% at May-12 while in the Head & Neck group ENT increases by 18% in May-12 and Ophthalmology increases by 70% in Jun-12. Note that admissions to Maternity includes all pre-partum care. There is no change in post-partum admissions.*

### 3.3 Effect on Occupied Beds

Fig. 2 explores the concept that the changes have a particular impact on bed occupancy. Bed occupancy has been divided into the medical group of specialties (general and elderly medicine, gastroenterology, cardiology, etc) while the non-medical group are mainly surgical specialties and trauma.

As can be seen, the number of beds occupied by medical group patients shows a step-like increase toward the end of May 2012. Occupied beds jump from  $335 \pm 16$  to  $389 \pm 16$  which represents a 16% increase. This figure is within the range of percentage increase in admissions noted to occur at the RBH in previous occurrences of these outbreaks, namely + 13% Mar-93, +18% Dec-96, +11% Jan-03, +13% Oct-07 [20]. Note the slight dip around Jan-13 followed by a late surge which is probably fueled by the late spread of the agent in certain affluent areas of West Berkshire [44]. The slight dip in non-medical occupied beds after May-12 is probably due to the reduction in elective overnight activity (Table 2), due to the serious bed pressures arising from this event. Hospitals in England are not paid based on bed occupancy, and there is no rational reason for the hospital to increase medical bed occupancy, indeed such an increase merely squeezes out elective overnight admissions, resulting in loss of income.

### 3.4 Diagnosis Specific Changes

Figs. 3 and 4 show the relative trends in admissions and deaths based upon diagnoses which 'are' and 'are not' affected by the presumed outbreak. As can be seen, both admissions and deaths associated with conditions not affected by the outbreak show a

continuous decline over time, while those which are affected show the characteristic step-like increase.

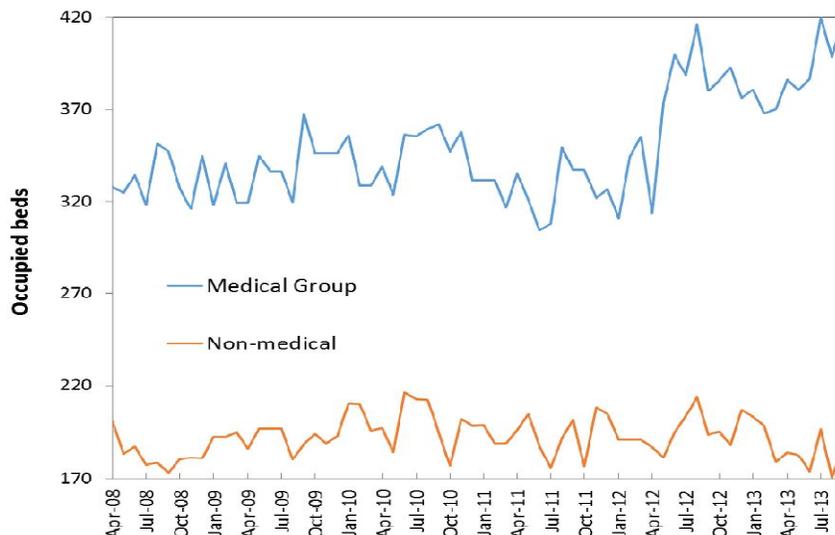
Due to the limited number of deaths occurring at the level of primary diagnosis, the broad analysis of *are* and *are not* affected was conducted at the level of Health Resource Group (HRG) group heading (first two digits), and this is presented in Fig. 4 where it can be seen that the increase in deaths is limited to specific HRG groups. HRG groups not affected were mainly related to surgical procedures and particular types of conditions (data not show). All other chapters are effected but some (especially respiratory), more so than others. Primary diagnoses where there were a sufficiently large number of admissions, were broadly grouped into 'are' and 'are not' affected by visual inspection of the running 12 month total, although the magnitude of the effect is variable between diagnoses. The important point to note is that for those conditions which are effected, both admissions and deaths rise in roughly parallel manner suggesting that the increase in deaths is *not* due to hospital-specific factors, but is due to 'push' into the hospital from the surrounding community, as has already been inferred from the previous sections.

Fig. 3 includes un-coded activity in the 'are effected' group, and it has been noted that on previous occasions of these outbreaks that ill-defined ICD codes especially R69 (Unknown causes of morbidity) and R99 (Unspecified causes of mortality) show a marked increase. The reason for this is fairly simple. The large and unexpected increases in medical admissions, and the ratio of FCE to spell accompanying these outbreaks overwhelms the coding process and these codes become default codes added to the un-coded activity in order for the hospital to gain income [8]. In this study, it is exceedingly difficult to implicate a reduction in the threshold to

admission when the additional admissions are confined to specific diagnoses in which deaths also show a near simultaneous and parallel increase, as was also demonstrated to occur in Wigan during the 2012 outbreak [43], and in the aftermath of the 2008 outbreak in South East Essex [42].

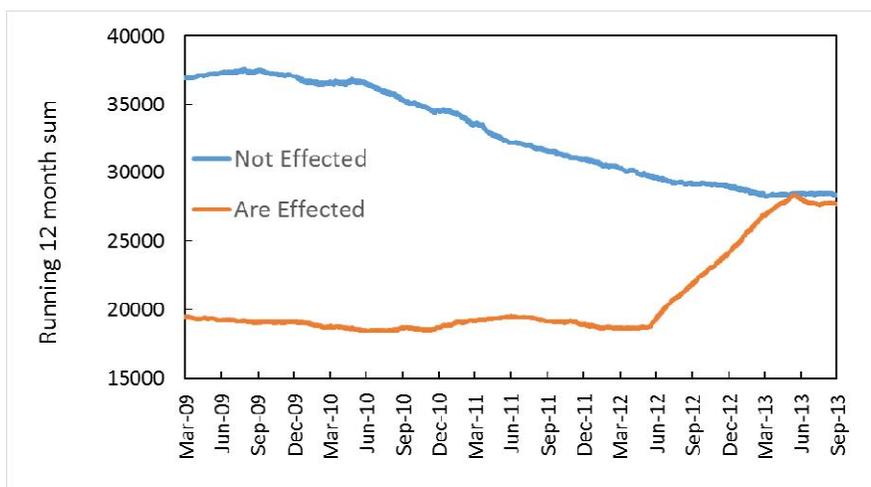
affected by the event continue to decline. As these conditions are treated in the same wards as the conditions showing an increase, it is very hard to envisage a situation where hospital-specific factors could be responsible for any of these trends. Indeed the 'push' for increased ED attendances and inpatient admissions seems to be external to the hospital (Fig. 1 and Table 2).

Indeed, it is important to note that both deaths and admissions (Figs. 3 and 4) for conditions not



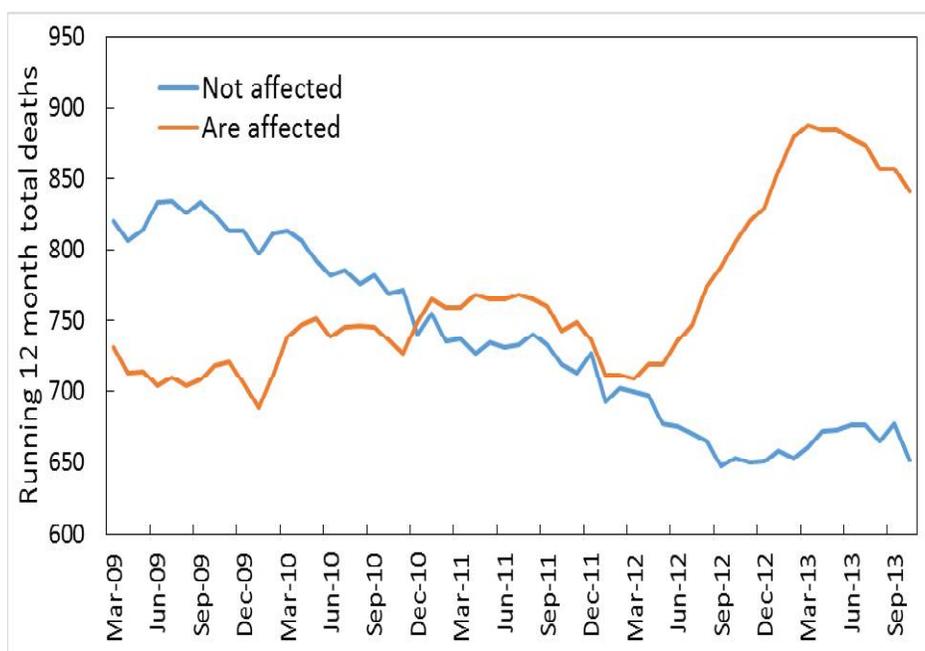
**Fig. 2. Seasonal-adjusted monthly average occupied beds (midnight)**

Occupied bed days for each month were divided by days per month to give occupied beds. Seasonal (month-of-year) adjustment was applied using an optimization method to minimize the successive difference between months. (editor...changed to 9 point)



**Fig. 3. Trend in admissions by primary diagnosis**

The 'are effected' group includes un-coded activity. In a running 12 month total the step-like increase occurs at the foot of the ramp.



**Fig. 4. Trend in deaths by HRG chapter**

*Note: The slight increase in the 'not affected' trend line commencing around Sep-12, is probably related to the difficulty of separating out all 'not affected' conditions by using the larger HRG chapters.*

### 3.5 FCE per Spell

In England, hospitals are paid on a per Spell basis, and hence there is no financial advantage to be gained by increasing the number of FCE per spell. At the RBH there was an increase in the number of FCE per Spell with around a 90% increase in 0 to 4 day stay FCE which occurs within diagnoses affected by the outbreak (data not shown). As can be seen in Fig. 5 the average FCE-based length of stay for the medical group dropped from around 6.5 to 4 days.

The fact that the ratio of FCE per Spell increased at the RBH is not necessarily universal, in that each health and social care system will react in its own unique way [8]. However, it is interesting to note that around the time of the 1993 event/outbreak a specific increase in the ratio of FCE to Spell was also noted to occur in the Avon region [64]. Re-appraisal of the data presented by Morgan et al. [64] reveals greater than a 35% increase in the slope of the trend line for FCEs either side of 1993/94, a step-like increase in persons admitted, and an intermediate increase in admissions. Interestingly, the data also shows evidence for the second of these events which occurred in 1996. Analysis of this second event is limited by the fact that the data ends in

1997/98. It can also be seen that the 1993 event did not reach the Avon region until the later part of the 1993/94 financial year, i.e. the issue of spatial spread. The specific and large increase in FCE noted above is suggestive of an increase in complexity, and similar increases in complexity (and complications) have been noted to occur in both Canada and the USA at times when these events appear to occur in these countries [65-69], and has been discussed in a recent review [8].

### 3.6 A Time Cascade for Deaths

The above expansion in FCE's can be used to increase the precision associated with the analysis of deaths, and diagnoses showing a particular increase are given in Table 5.

The results in this table are both FCE- and Spell-based. For Spell-based analysis the primary diagnosis has been taken from the first FCE in the admission while the FCE-based analysis utilizes the primary diagnosis reported for all FCE within the Spell, which implies that each death will be counted more than once depending on the number of FCE per spell. The FCE-based percentage increase has then been adjusted downward by the ratio of FCE per Spell to

remove the effect of double counting and give two estimates for the percentage increase in deaths. Hence after the step-like increase, for those who have died, there are around 1.9 FCE per spell although this varies depending on the admitting diagnosis. Note that there appears to be a condition-specific time cascade regarding the point at which deaths show the step-like increase.

This is a small study and many of the increases are not statistically significant, however, the aim has been to illustrate the possibility of a disease time cascade emanating out of these outbreaks. This requires confirming studies using larger data sets than those for a single hospital.

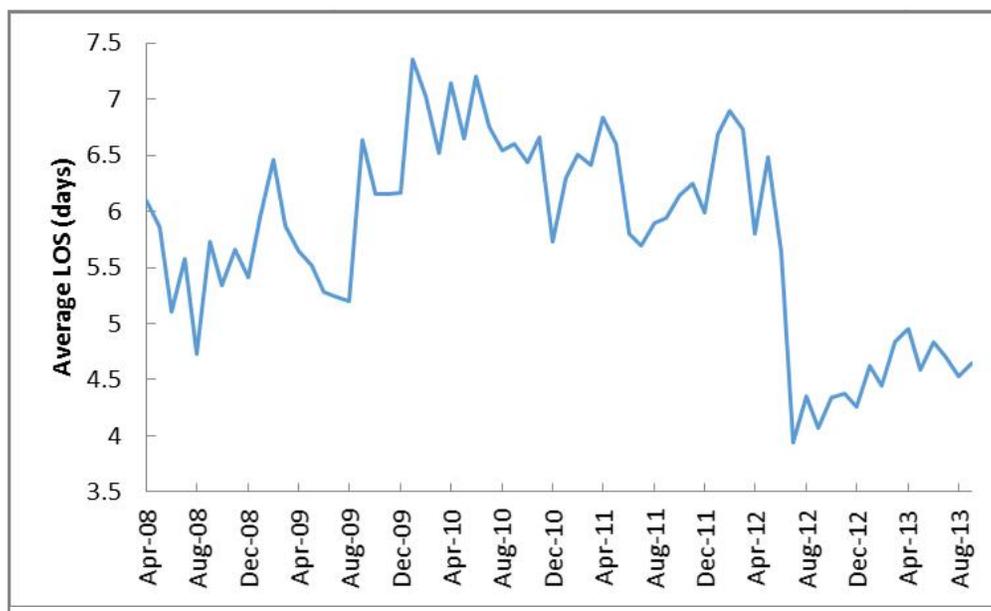
At the level of primary diagnosis, there were sufficient deaths (>100 per annum) within the top five primary diagnoses to conduct analysis of trends at daily level, and the following points of initiation were noted (date of maximum step-like increase in brackets, ICD-10 3 digit primary diagnosis code at the start): N39 urinary tract infections (16<sup>th</sup> April 2012), I50 congestive heart failure (7<sup>th</sup> April 2012), A41 sepsis (29<sup>th</sup> July 2012), J18 pneumonia (20<sup>th</sup> May, 2012), and I63 cerebral infarction (1<sup>st</sup> August 2012). For these diagnoses the date associated with the maximum increase was determined using a running 365 day total, and this more precise method gives

initiation points with greater time precision than the less precise dates in Table 5 derived from a running 12 month total. However the spread in dates is suggestive of a progressive process which depends on the particular condition.

### 3.7 Effect of Age

Previous studies on this phenomenon have indicated that there are specific single-year-of-age patterns in both admissions and deaths [19,42-43]. This type of effect can be due to exposure to a time series of different strains of the same infectious agent. Figs. 6 and 7 investigate the effect of year of age on the change in deaths and admissions respectively. Single-year-of-age specificity is evident in both Figures, however, in Fig. 7 this single-year-of-age specificity is also shown to apply to the timing of the increase. Table S2 in the supplementary material gives greater detail regarding age, initiation date and percentage increase in admissions.

Whatever the eventual explanation we are clearly dealing with a complex phenomenon which defies all attempts to suggest that the effects are due to the actions of the hospital, and certainly go far beyond trivial explanations based on reductions in the threshold to admission.



**Fig. 5. Trend in medical FCE-based average length of stay (emergency)**  
 Total bed days per month for the medical group of specialties were divided by FCE per month to give the FCE-based average length of stay.

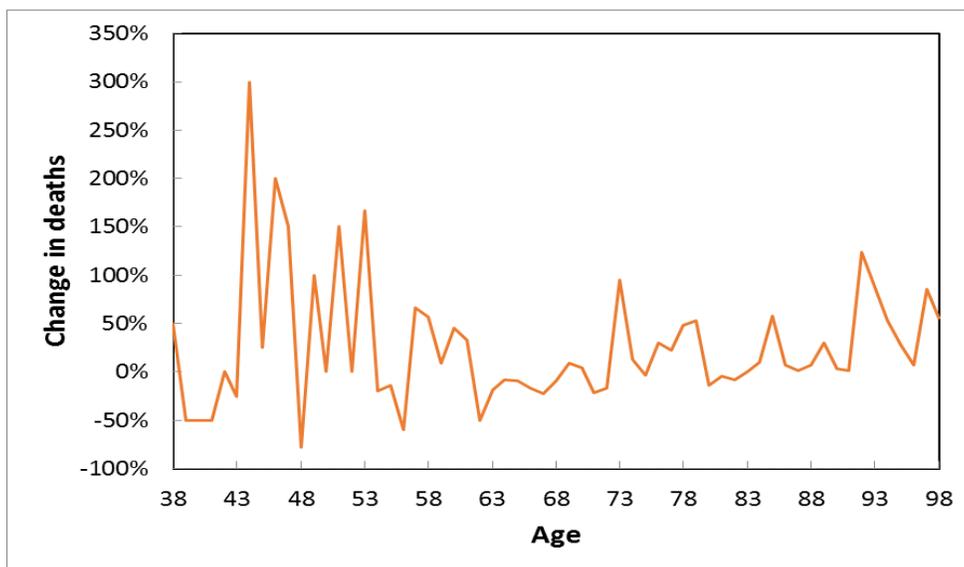
**Table 5. Diagnoses and condition groups with a step-increase in deaths**

Diagnosis	Deaths	FCE:Spell	Increase (%)		97.5% CI	Start
			FCE	Spell		
All Cancers	169	2.12	11%	0%	16%	Jan-12
All Intestine/peritoneum	23	1.09	71%	23%	48%	Jan-12
All Liver/hepatic diseases	28	2.21	61%	94%	36%	Feb-12
All Diabetes	6	1.50	50%	13%	62%	Feb-12
All Asthma/Bronchiectasis	5	1.80	153%	200%	62%	Feb-12
All Cardiac arrest & heart failure	74	1.78	31%	23%	27%	Mar-12
All Intestinal vasculitis/colitis	19	2.84	17%	24%	38%	Mar-12
Interstitial pulmonary diseases with fibrosis	6	2.67	90%	150%	53%	Mar-12
Congestive heart failure	41	2.05	58%	55%	32%	Apr-12
Urinary tract infection	53	1.70	131%	93%	32%	Apr-12
All COPD	47	1.72	128%	104%	33%	Apr-12
COPD with acute lower respiratory infection	31	1.81	226%	133%	37%	Apr-12
All Complications & after care	6	2.67	197%	300%	53%	Apr-12
<b>Total</b>	<b>1,510</b>	<b>1.88</b>	<b>37%</b>	<b>12%</b>	<b>5%</b>	<b>May-12</b>
All Pneumonitis/other lung/failure	59	2.39	15%	0%	26%	May-12
All Renal and nephritic disease	57	1.96	114%	110%	29%	May-12
Acute renal failure, unspecified	46	1.67	119%	108%	33%	May-12
Pneumonitis due to food and vomit	30	2.20	23%	0%	35%	May-12
All other neurodegenerative diseases	25	1.56	153%	93%	42%	May-12
All diagnoses less than five deaths per annum	464	1.65	46%	0%	9%	May-12
All Signs & symptoms	60	1.30	176%	205%	33%	May-12
All Pneumonia	357	1.89	59%	25%	10%	Jun-12
Lobar pneumonia, unspecified	176	1.96	99%	60%	17%	Jun-12

**Table 5 Continued .....**

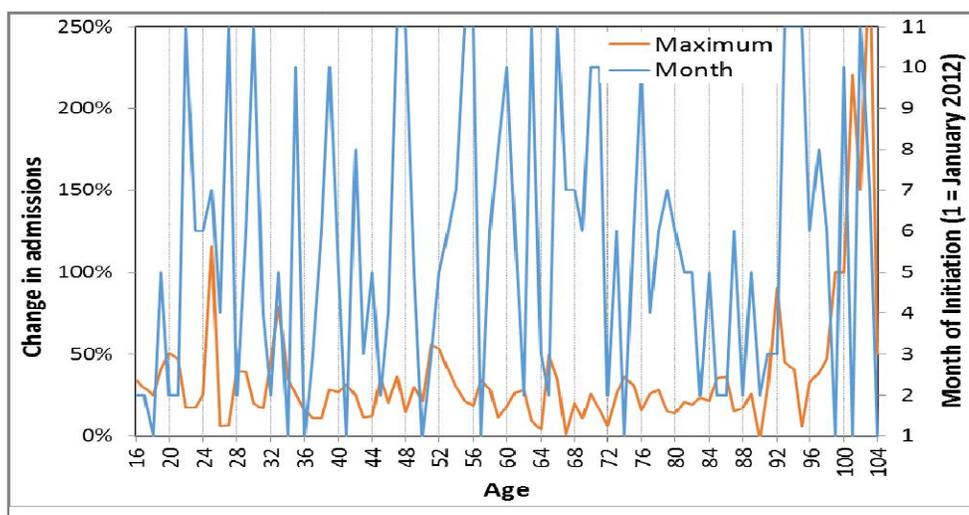
Pneumonia, unspecified	113	1.84	39%	17%	22%	Jun-12
All Myocardial infarction	36	1.83	47%	31%	35%	Jun-12
Unspecified acute lower respiratory infection	25	1.56	396%	383%	42%	Jun-12
Gastrointestinal haemorrhage, unspecified	13	2.00	89%	71%	47%	Jun-12
COPD with acute exacerbation	13	1.62	132%	133%	50%	Jun-12
All Cerebral haemorrhage/infarction/stroke	109	1.74	23%	0%	23%	Jul-12
Sepsis, unspecified	45	1.78	72%	69%	33%	Jul-12
All Sepsis	60	1.93	63%	59%	29%	Jul-12
Cerebral infarction, unspecified	53	2.06	37%	14%	29%	Jul-12
Blank/Uncoded	43	2.05	70%	46%	32%	Jul-12
All Infections excluding sepsis	26	1.73	99%	145%	40%	Jul-12
All Skin	20	1.55	312%	233%	45%	Jul-12
All Fractures & wounds	62	1.50	30%	5%	31%	Aug-12
All Dementia/Alzheimer/Parkinson's	15	2.00	57%	36%	45%	Sep-12

*The count of deaths is given as an indication of relative number of deaths per annum and are from the twelve months October 2012 to September 2013. For cancers the start lies in the interval January to June 2012 – probably due to the huge variety of cancers. Many diagnoses have been lumped into a condition group such as 'All Skin' simply because there are too few individual diagnoses.*



**Fig. 6. Change in deaths by year of age**

*Change in deaths were determined for the 12 month period ending May 2012 versus May 2013.*



**Fig. 7. Change in admissions and month of initiation by year of age**

*The 'Maximum' change in admissions refers to the value of the step-like increase in admissions which occurs at the month of initiation, as determined by a running 12 month analysis.*

#### 4. DISCUSSION

This section will attempt to place the above findings into a wider context. Firstly, this work appears to confirm earlier studies which suggest that it is the absolute number of deaths (rather than standardised death rates) which drive the incremental changes in demand for hospital beds and health service costs rather than demography *per se*. Hence these outbreaks become both a national and local source of long-term cycles in

financial pressure leading to cycles in NHS surplus and deficit [42,46,49-50].

The next issue to be addressed is the explanation of why deaths would increase, thereby leading to the increase in admissions in the interval prior to death. It has been proposed that this behaviour, along with the associated cycle in the gender ratio at birth, arises from a genuine infectious outbreak [1,8-10,51]. In just the same way that infection with HIV/AIDS is

associated with clusters of secondary infection(s) and susceptibility to particular cancers [87], the agent behind these outbreaks appears to affect a wide range of medical conditions (including post-operative complications) whose common linkage appears to be their ability to be manipulated via the balance between inflammatory and autoimmune forces. This working hypothesis has been the subject of a number of reviews of the available evidence [8-10,16,18,78] and may even include knock-on effects against conditions such as appendicitis [92]. A reasonable match between the diagnoses which increased during the 2002 and 2007 outbreaks, and the diagnoses associated with death following hospital admission subsequent to the 2007 and 2012 outbreaks, has been made with the known immune modulating effects of the ubiquitous herpes virus, cytomegalovirus (CMV), especially against elderly persons [8,10,18,70], and with the recognised wider role of CMV to increase the odds ratio for death in particular conditions such as cardiovascular disease, respiratory conditions, cancers [see reviews 8,10,18,78,92].

Both the increase in emergency admissions and deaths are well within the known limits for an increase in infected persons via infectious spread of this virus (23). Somewhat surprisingly CMV has fairly potent inflammatory effects against the eye, especially in the elderly [71-76], and this appears to be reflected in the large increase in ophthalmology admissions (Table 4), although the apparent large percentage increase is against a very low number of admissions before the event. A similar case can be made for ENT admissions [77]. Infection of the lungs, nervous system and gastrointestinal tract with CMV are common and can explain the large increase in particular medical admissions [70]. An additional cluster of increased admissions for those with rheumatologic and joint disorders (data not shown), likewise relates to the known ability of this virus to exacerbate inflammation in autoimmune conditions [78]. Indeed the top five primary diagnoses associated with death are all highly related to the known effects of CMV as reported in hospital case studies [70,78]. The progression in dates for maximum onset commencing in April 2012 (Heart failure and Urinary tract infection), May (pneumonia), July (Sepsis) and August (cerebral infarction), is once again highly suggestive of disease progression which would arise from an infection with an immune modulating and primarily inflammatory basis.

Analysis of Hospital Episode Statistics (HES) data for England has led to the suggestion that emergency Oncology admissions may actually peak one year after the initiation of the outbreak [79]; admissions for the more aggressive types of tuberculosis appear to peak three years after the outbreak [80], allergy admissions show a lagged increase after nine and 22 months [81], and depending on age neurological conditions also show evidence for lagged increases in admissions [17]. In the USA certain CMV-sensitive cancers appear to follow cycles originating in these outbreaks [82]. In addition, specific changes in outpatient and emergency department case-mix are associated with both the 2008 and 2012 outbreaks [83-86] – the shift being toward immune sensitive conditions (infection, inflammation and auto-immunity). It would appear that immune-mediated disease time cascades are a particular outcome of these outbreaks. Whether the agent responsible for these outbreaks is indeed CMV remains to be determined, but CMV would almost certainly take opportunistic advantage of such an immune-modifying infection, as it does in the case of HIV/AIDS [87], and such opportunism would impose a degree of CMV-like nature on the outbreak. Urgent research is required to isolate the exact infectious agent.

Increases in in-hospital deaths are usually considered indicative of potential poor hospital care [88-89], and it has been pointed out elsewhere that these outbreaks and their associated spatial spread have enormous implications to the calculation of hospital standardised mortality rates (HSMRs) [13,19]. I have observed that both the Royal Berkshire and other hospitals appear to have been flagged specifically for pneumonia as HSMR outliers at the onset and during points in the local outbreak, i.e. the spatial spread of the outbreak leads to a situation where deaths at a local level are out of synchrony with the national average, and Table 1 is a useful aid to envisage this situation. In this respect pneumonia is probably the only diagnosis with enough admissions (Table 5) for the HSMR methodology to detect a significant change. The increase in cancer deaths noted in Table 5 was a repeat of the situation noted in national data following the 2008 outbreak [13] and CMV was once again implicated. This research merely suggests that the calculation of HSMRs may be more complex than realised.

The issue of single-year-of-age specificity has been raised in four other studies [19,42-44] and

appears to be supported by this study (Figs 6 & 7). This study has extended this relationship to show that there also appears to be some form of single-year-of-age specificity regarding the time of onset as well as the extent of the effect. Such timing effects could arise from clusters of case mix associated with different ages (see Supplement) plus the immune priming effects arising out of previous exposure to different strains of the infectious agent [19].

The apparent clustering in the area-wide results observed in admissions at hospital level need to be considered. The agent responsible for these outbreaks enters the UK toward the middle of 2011 in Scotland and parts of England [1,41,90], and will be spread via movement of people to and from these early sites. While the spread of the agent has been shown to result in rapid increases in admissions from small spatial areas, it is important to realise that at hospital level what is seen is the result of the total spread of the agent.

In the case of the Royal Berkshire hospital this is illustrated in Fig. 8 by taking the trends in death in the surrounding LAs both individually and as a composite for the hospital as a whole, where the totality of medical admissions is roughly comprised of admissions from each of the LAs: Reading (37%), Wokingham (36%), West Berkshire (15%), South Oxfordshire (10%),

Others (2%). On this occasion the time span covers both the 2008 and 2012 outbreaks. Note the very strong response to the 2008 outbreak in Windsor & Maidenhead, while Wokingham has a lesser response to the 2008 outbreak and a far higher response to the 2012 outbreak. The response observed from the perspective of the Royal Berkshire hospital is a broader and less specific peak for the 2008 outbreak, and a somewhat clearer response to the 2012 outbreak, although on both occasions these are a composite of the parts. Issues relating to small-area spread across Berkshire are presented in an accompanying paper [44].

However, the exact effect upon admissions observed at the hospital is likely to be even more complex. For example, persons (especially the more vulnerable by virtue of age/condition) will become infected at all points commencing from the start of the outbreak in Berkshire around the middle of 2011 [44]. The impact of such infection may not reach a 'mass effect', as seen at LA level in Fig. 8, until a significant number of people have been infected. This however does not prevent a gradual rise in admissions which are focussed from all surrounding areas at the hospital. For example, visual examination of the data shows that the initiation point sometimes occurs over two to three months, and the 'initiation date' reported here is merely the point of maximum step-like change.

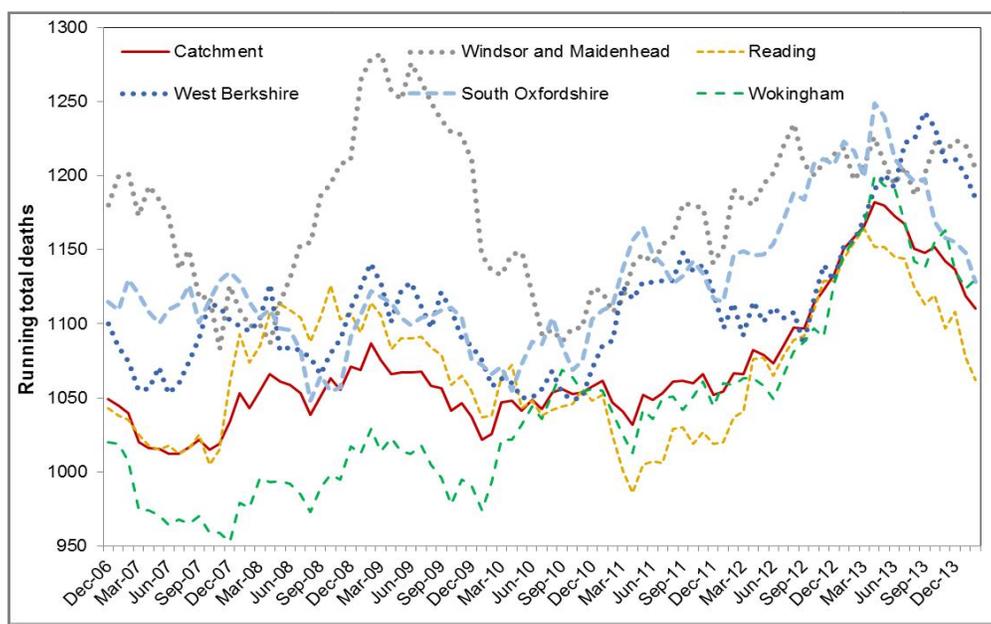


Fig. 8. Running 12 month total deaths in surrounding Local Authority (LA) areas and a composite picture reflecting the hospital catchment area

The issue of the complex patterns relating to age and condition/timing suggest that some form of theoretical modelling is needed to unravel what is being observed at hospital versus small-area level. The agent responsible must of necessity be capable of complex interactions. For example, if CMV were the agent, it is known that there are multiple sexual and non-sexual transmission routes [91], infection severity interactions between multiple strains, and other infectious agents and a spectrum of disease enhancement including cancers, all layered on top of potential genetic predispositions [8,10,18,92]. For the moment this virus remains a useful working model.

Finally it needs to be pointed out that much recent health care policy in England relies on the assumption that care will be shifted out of an acute setting into community-based schemes. Such policy initiatives rely on the further assumption that the demand for community care remains reasonably constant to match with fixed community health and social care staffing. Were a large infectious event to occur these fixed resources would be overwhelmed and acute care would once again become the default response [93-96]. This would be especially the case were the infectious event to result in large numbers of persons suddenly approaching the end of life in a synchronous way. Hence while it may be desirable to move care out of an acute context, a degree of realism needs to be expressed as to the flexible nature of the resources that may be implied in maintaining such schemes [96].

In the past it has been assumed that the increase in emergency admissions is related to declining thresholds to admission [36] and hence the 70% reduction in the tariff for emergency admissions above a 2009/10 baseline was introduced in England in the aftermath of the 2007 event (which spread across England during the end of 2007, throughout 2008 and into 2009 [13,62]. However it is exceedingly difficult to implicate a reduction in the threshold to admission when the additional admissions are confined to specific diagnoses in which deaths also show a near simultaneous increase. It needs to be pointed out that the conclusions reached by the Nuffield Trust report were in fact flawed. The authors argued that a decline in the number of admissions ending in a death over the period 2004 to 2009 was evidence for a reduction in the threshold to admission. The unfortunate fact is that the absolute number of deaths in England

(all-cause mortality) has been declining since the mid-1990's due to a continuous reduction in the mortality rate. Hence by using the 2004/05 rates of death they inadvertently failed to account for the overall decline in mortality rates. For example, between 2004 and 2007 male deaths declined by around 2.3% while female death declined by 3.3% which accounts for the supposed gap identified in the Nuffield Trust report. This is an example of the constant risk fallacy. Furthermore these authors did not appreciate the fact that the apparently confusing jumble in the extent of increase in emergency admissions over time which they observed, was in fact, arising out of infectious-like spatial spread of both deaths and increased medical admissions.

In the study of Morgan et al. [64] in the former Avon region of south west England over the nine year period 1989/90 to 1997/98, which encompassed two of these events/outbreaks, some 57% of the rise in emergency admissions could not be accounted for by demographic change. A similar unaccounted increase in adult appendicitis has also been noted to occur in England, with inflections in the trend line apparently associated with these outbreaks [92].

Some form of population or societal effect can likewise be discounted due to the fact that it is only those emergency department attendances which result in an admission which show a specific increase. Note that the use of a running total in Figs. 1, 3 and 4 implies that the point at which the slope changes around February to June 2012, indicates a sudden step-like increase in attendances resulting in an admission. This step-like increase has to endure for a full 12 months to maintain a constant ramp, such that the full extent of the step change is revealed at the point 12 months on from the initiation of the change in slope.

Indeed it is important to note that both deaths and admissions (Figs. 3 and 4) for conditions not affected by the event continue to decline. As these conditions are treated in the same wards as the other conditions showing an increase it is very hard to envisage a situation where hospital-specific factors could be responsible for any of these trends. Indeed the drive for increased ED attendances and inpatient admissions arises external to the hospital, as is demonstrated in the accompanying paper on small-area spread throughout Berkshire [44].

## 5. CONCLUSION

Evidence has been presented for highly unusual behaviour in medical admissions, occupied medical beds and in-hospital deaths associated with the seeming spread of an infectious agent across Berkshire commencing in 2012 and continuing into 2013 [44]. The infectious-like behaviour is highly condition- and age-specific both in terms of the magnitude and timing of the effect. The trends defy all common explanations based on hospital-based inefficiency or societal factors. It would appear that we have a significant new public health challenge which requires appropriate responses rather than insisting that the 'problem' is all to do with the inability of NHS organisations to 'manage' demand. While such simplistic views may be conveniently suited to the supposed levers of government policy, on this occasion, they are clearly not working in the real world. The tendency of politicians to ignore contrary evidence and to select evidence confirming policy, the 'policy based evidence' effect [97], may have had a strong role in explaining why this and other evidence has been repeatedly ignored.

There are obvious implications to the calculation of HSMR using single-year-of-age adjustment for particular diagnoses especially during the periods of granular spread of the agent across the UK.

An accompanying paper in this journal presents the evidence for small-area spread of the infectious agent across the whole of Berkshire during the time where admissions and bed occupancy increased at the Royal Berkshire hospital [44], i.e. this is part of a far wider phenomena and is not isolated to a single-hospital or single location. A further paper investigates spread, involving increased death, across England and Wales during the same time period [90].

While an infectious agent has been implicated, in this and previous outbreaks, the exact agent remains to be identified. The immune modifying herpes virus, cytomegalovirus (CMV), has been circumstantially implicated, but this requires further study to confirm if CMV is merely re-activating in the presence of another infectious agent, or if CMV is the primary infection, perhaps via the introduction of a new strain, or indeed if an entirely different agent is involved.

Based on past patterns the next outbreak is due somewhere around 2016 to 2018 and urgent preparation is required to document this forthcoming event in greater detail.

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## CONSENT

Not applicable.

## ETHICAL APPROVAL

Not required. No patient identifiable data was used in this study. Data extracts were provided by the RBH NHS FT. Permission to publish this work was obtained from the RBH NHS FT.

## COMPETING INTERESTS

Authors have declared that no competing interests exist. There were no sources of funding.

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