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Small Area Spread of a New Type of Infectious Condition across Berkshire in England between June 2011 and March 2013: Effect on Medical Emergency Admissions

Rodney P. Jones[1*] and Sid Beauchant[2]

[1]Healthcare Analysis and Forecasting, Camberley, GU15 1RQ, UK.
[2]Berkshire Healthcare NHS Foundation Trust, 57-59 Bath Road, Reading, RG30 2BA, UK.

Authors' contributions:

This work was carried out in collaboration between both authors. Author RPJ designed the study, and wrote the first draft of the manuscript. Author RPJ managed the literature searches, author SB managed all data acquisition, including sourcing environmental and population data, author SB performed analysis involving MapInfo, both authors contributed to analysis. Both authors read and approved the final manuscript.

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ABSTRACT

Aims: This study aims to investigate the small area spread of a presumed infectious agent, and to determine which factors determined the point of initiation, speed of the spread and the resulting increase in emergency medical admissions.
Study Design: Analysis of a monthly time series of medical admissions using small area population aggregates of around 7,000 population contained within the census spatial unit called a Mid Super Output Area (MSOA).
Place and Duration of Study: Emergency medical group admissions for residents of the six unitary authority locations in Berkshire, southern England between January 2008 and March 2013.
Methodology: A running twelve month total of admissions was used to determine the point of

**Corresponding author: Email: hcaf_rod@yahoo.co.uk;*

initiation and the extent of a step-like increase in medical admissions.
Results: Analysis shows evidence for spatial spread initiating around June 2011 through to March 2013. At onset, medical admissions increase and stay high for 12 to 18 months before beginning to abate. This spread commenced earlier among mainly Asian small areas (clustered from July 2011 onward) and later (clustered around March 2012) in predominantly affluent white areas. The observed percentage increase in admissions within the unitary authority areas varied from 25% to 51% (median value), however the average increase was highest as the geographic area became smaller, and this is suggested to arise from the aggregation of smaller social networks where the point of initiation of infectious spread occurs over time. The percentage increase in admissions displayed high single-year-of-age specificity suggestive of the immune phenomena called antigenic original sin, and is therefore suggestive of a different strain of an agent with previous outbreaks. The increase in emergency admissions showed a month-of-year pattern which appeared to follow the seasonal pattern of vitamin D levels in the blood. The presence of nursing homes, deprivation and ethnicity also has an effect on the average increase in admissions.
Conclusion: It is suggested that all the above point to an outbreak of a previously uncharacterized type of infectious agent. There are profound implications regarding the use of standard five year age bands for the standardization of medical admission rates.

Keywords: Spatio-temporal spread; hospital medical admissions; emerging infectious diseases; vitamin D; ethnicity; deprivation; care homes; cytomegalovirus; infectious spread; age standardization.

1. INTRODUCTION

A trend to far higher than expected emergency department attendances and medical admissions has been noted across Western countries over many years. Explanations for this have focused on the breakup of the nuclear family, the elderly living alone, higher expectations from health care and a reduction in thresholds to refer by GP's and to admit to hospital [1]. It has been recently pointed out that the increase is not gradual, as would be expected from societal factors, but occurs in bursts of growth which appear to coincide with unexplained periods of higher death [1].

In early 2012 deaths (all-cause mortality) in England and Wales experienced an unexpected and unexplained increase which endured for around 24 months [2-4]. This same trend was observed to occur slightly earlier in Scotland, where it is a repeat of a similar pattern observed to initiate in 1993, 1996, 1999, 2002 (deaths in the UK peak in 2003) and 2007 (deaths peak in 2008) [3]. The increase in deaths in England shows very high granularity at local authority (LA) level [2,4], however as can be seen in Table 1, parts of Berkshire and adjoining LA's experienced some very high increases while others show little effect (at least in 2012). Poisson randomness is unable to explain the wide range in the increase seen between LA's [2]. As can also be seen in Table 1 the increase in deaths tends to be higher where there are greater proportions of elderly people, which suggests the possibility of elderly-to-elderly transmission or higher acuity of effect in the elderly, perhaps dependent on age.

The fact that there are more elderly people in a location should not, in itself, lead to an unexplained percentage increase in the number of deaths between 2011 and 2012, except where the agent responsible for the increase shows single year of age-specificity [5]. In addition to the above, spatial spread of deaths in LA's across England, Wales and Scotland, has been demonstrated to be associated with the 2012 event [4-6], and the increased deaths show single-year-of-age saw-tooth patterns which are reminiscent of the effects of 'original antigenic sin', i.e. the process whereby the immune system is primed by exposure to a recurring series of infections by different strains of the same agent [5]. The excess deaths in 2012 were also gender and condition specific [7-10]. All of the above suggest a type of infectious event.

It has been observed that these events are also associated with an unexplained increase in medical emergency admission, emergency department attendance (ED) including sudden shifts in case-mix, total healthcare costs, and to a more variable extent in GP referral for an outpatient attendance [1,3,9-11], all of which show spatiotemporal granularity and spread consistent with an infectious-like outbreak [1-5, 9-11]. For example, emergency department

attendances in Bromsgrove and surrounding locations in the West Midlands, which experienced a 28% increase in age 80+ deaths (the highest in England) [12], led to the situation where ED's in this location were among the first to report unusually high levels of attendance and emergency admissions in 2012 [13], which continued into early 2013 [2].

In the past, such increases in emergency admissions (which are mainly confined to the medical specialties) have been partly attributed to a reduction in the acute threshold to an admission [14]. However, this is unable to explain the near simultaneous increase in deaths and GP referrals [2,15-16] and contradicts research conducted in the USA which demonstrates that acute hospital thresholds to admission are maintained despite large fluctuation in admission rates, and that the resulting bed pressures are balanced by flexing the threshold to discharge [17], which although this accommodates increased admissions, it is not an explanation for them.

In an attempt to explain this curious behavior, which also appears to be international in scope [1,4,9], it has been suggested that the root cause may be an outbreak of a previously unidentified infectious agent. Evidence for spatial spread between small areas (i.e. approximately 7,000 head) of an infectious-like agent, has been recently presented following the previous 2008 event in North East Essex [18], and for the 2012 event in Wigan on the outskirts of Manchester [19]. This work builds upon the existing small and large area studies, and examines the pattern of increase in medical admissions between small area populations using census-based aggregation of population groups into mid super output areas (MSOA) across the ceremonial county of Berkshire in Southern England. This represents a larger geographic area than the earlier small-area studies, and contains a far more diverse mix of ethnic minority groups along with pockets of high deprivation. This study supplements additional analysis of the impact of this outbreak at the Royal Berkshire Hospital situated in Reading, in the western part of Berkshire [20].

Table 1. Increase in deaths in 2012 versus 2011 for Berkshire and surrounding Local Authorities

Local Authority	Age 40+	Age 60+	Age 80+	± 1SD	Proportion age 65+	Initiation Date
South Buckinghamshire	14%	18%	21%	3.3%	19.4%	Dec-11
South Oxfordshire	9%	11%	16%	3.0%	18.2%	Jan-12
Reading	**12%**	**13%**	**13%**	**3.3%**	**11.5%**	**Jan-12**
Wokingham	**9%**	**10%**	**11%**	**2.8%**	**15.4%**	**Jun-12**
Wycombe	3%	4%	11%	3.2%	15.8%	Aug-12
Bracknell Forest	**4%**	**8%**	**10%**	**3.3%**	**12.5%**	**Jul-11**
Surrey Heath	5%	2%	9%	3.7%	16.7%	Jun-12
West Berkshire	**1%**	**3%**	**7%**	**3.1%**	**15.4%**	**Sep-12**
Windsor & Maidenhead	**7%**	**7%**	**5%**	**3.0%**	**16.7%**	**Aug-11**
Basingstoke & Deane	0.3%	-0.8%	4%	3.0%	14.4%	Mar-13
Slough*	**-3%**	**-4%**	**3%**	**3.3%**	**9.1%**	**Jun-11**
Hillingdon	8%	7%	3%	2.5%	12.8%	Jan-12
England	3.3%	3.8%	5.7%	0.2%		
England (top 80 LA's)	8.0%	9.0%	13.6%	0.3%		
England (bottom 80 LA's)	-1.1%	-1.0%	-1.4%	0.3%		

Calendar year data is from Office of National Statistics. Standard deviation (SD) is from Poisson variation for the 40+ increase, although this figure roughly applies across all ages. Population is mid-2011 based census estimates, and the proportion aged 65+ has been calculated to indicate which locations contain more elderly persons. Local Authority areas in Berkshire are in bold. Initiation date is from the study of Jones [4] using monthly deaths. (*)Determining the exact initiation date for the increase in deaths in Slough is obscured due to the tail-end of another outbreak which may have been triggered by the 'swine flu' epidemic [4]. The initiation date for the increase in medical admissions has therefore been used in this table. Death should be a lagging rather than leading indicator since the opportunity for admissions are terminated by decease

2. DATA AND METHODS

Counts of calendar year and monthly deaths for LAs in 2011 and 2012 were obtained from the Office for National Statistics (ONS). This data has been used to construct Table 1 in the Introduction section.

Emergency (non-elective) medical admissions for each month over the period January 2008 to March 2013 were extracted from the data warehouse. This study did not employ patient identifiable information and only used aggregate number extracts at MSOA level and by age for the whole of Berkshire. The separation of the extracted data from that within the data warehouse was enforced by the data custodian. Medical admissions were defined as an admission to any one of 40 specialties of a medical nature (see supplementary material). While this list appears to be extensive, the majority of admissions are to general and elderly medicine, cardiology, gastroenterology and rheumatology. Specialty 180 (Accident & Emergency) has been included since many hospitals use this specialty code to record direct admissions into medical assessment units. General & elderly medicine plus A&E (medical assessment), account for over 75% of these admissions, and the other specialties range from 4.4% to less than 0.1% of the total. A summary of the MSOA level data is available in the supplementary material.

Single year of age population for males and females by MSOA was from Office for National Statistics (ONS) and is based on the mid-2011 census population, i.e. the reference year before the step-like increase.

Data on percentage ethnic groups was from ONS 2011 Quick Statistics (QS201), overcrowding from Quick Statistics (QS409). The 2010 MSOA Index of Multiple Deprivation (IMD) values were from North East Knowledge & Information Team, Public Health England. MSOA population centroids from ONS geography, and distance to the M4 motorway via special query within MapInfo Professional. Nursing home postcodes from Care Quality Commission (2013) linked to MSOA using MapInfo Professional. Air pollution (PM10 and nitrogen dioxide) for Reading monitoring site from uk-air.defra.gov.uk and temperature for Emmbrook in Wokingham (Berkshire) from www.woksat.info (Mr Bernard Burton).

MSOAs containing a preponderance of admissions to Heatherwood and Wexham Park hospitals NHS Foundation Trust during the months of August, September and February in the 2012/13 financial year, were corrected for undercounting due to IT problems affecting admissions via the emergency department (ED). Values were corrected to a best estimate from time trends.

Monthly data on admissions was cumulatively totaled using a running 12 month sum. This method is suited for the analysis of step-like changes where the initiation of the step change is at the foot of a 12 month long ramp, and the extent of the change is at the point 12 months after the foot [21]. The point at which the maximum was reached was determined using the ratio of successive twelve month periods. A visual check was then performed to see if this marked the point 12 months on from the foot of the ramp.

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. 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% CI = $(1.965 \times N^{-0.0891})-1$. This equation was then used to calculate the 97.5% CI associated with the step-increase observed in the various locations. Given the fact that a Poisson distribution becomes less skewed at higher numbers, when N> 1,000 then the 97.5% CI = $2.7 \times n^{-0.5}$ [18].

3. RESULTS AND DISCUSSION

3.1 Background

In the UK all Census data is collected at output area (OA) level, and this is then aggregated up to larger spatial units which nest within the boundaries of a Local Authority (ILA). MSOA aggregated data has been used in this study since it gives sufficient medical admissions to enable statistically significant analysis. There are 7,200 MSOA in England and Wales, and this study relates to the 107 MSOA within Berkshire. An MSOA in England and Wales typically contains around 7,600 population (range 2,220 – 16,400), of which around 1,250 are aged 65+

(range 50 – 4,400). MSOA in Berkshire tend to lie toward the median values.

In any study of this nature it is necessary to demonstrate that the observed changes are statistically significant. All step-like increases in emergency admissions exceeded the 97.5% confidence interval (CI) from Poisson statistics. The MSOA with the fewest admissions was E02003452 with 330 admissions per annum before the 81% step-like increase seen for this MSOA. The 97.5% CI was ±17% hence the increase of 81%±17% was highly significant. The MSOA E02003432 with 741 admissions per annum before the step-like increase had the highest CI relative to the step-like change of 15%±9%, hence even in the worst case all changes were significant, and could not arise from simple Poisson variation. Similar results have been demonstrated in the two previous small-area studies [18-19], although the generally higher population density in Berkshire has enabled greater statistical significance.

3.2 Step-like Increase

Fig. 1 demonstrates the dramatic change in emergency medical admissions seen at LA level across Berkshire during 2012. In a running 12 month total chart the onset of a step-like increase is marked at the foot of a ramp lasting 12 months, i.e. each month increment in the running total adds more months of data containing the increase in admissions.

The full extent of the step-like change is therefore revealed in the running total at the point 12 months after the initiation point. The effect of the agent leading to the step-change must endure for a minimum of 12 months, otherwise the ramp will be truncated. As can be seen, the point of initiation is slightly different, as is the extent of the increase across the different LAs. This high-level picture is repeated for individual small area locations (MSOA) within each LA, and the median for both the increase in admissions and initiation date are shown in Table 2.

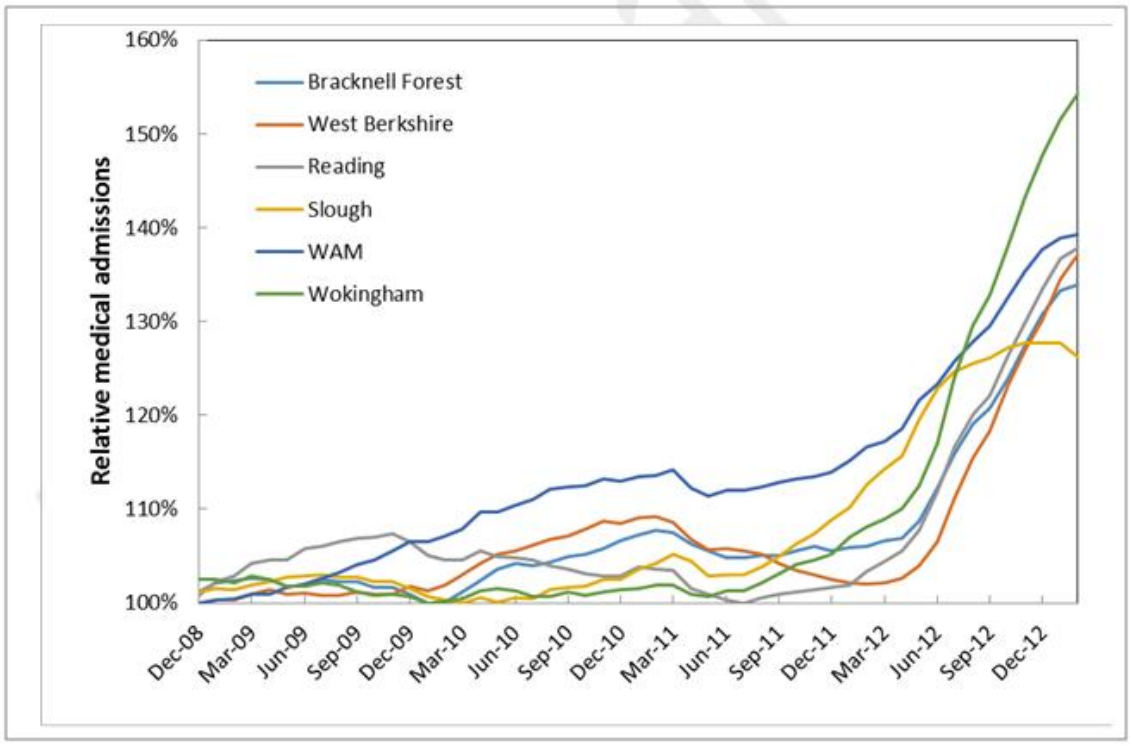

Fig. 1. Trend in running twelve month total medical admissions for residents of Berkshire Local Authorities

Residents of Slough, northern parts of Windsor, Ascot and Maidenhead (WAM) and Bracknell Forest mainly flow to Wexham Park hospital (Slough). Southern parts of WAM and Bracknell Forest (BF) mainly flow to Frimley Park hospital (Camberley, Surrey), while Reading and western parts of BF, most of Wokingham and eastern parts of West Berkshire mainly flow to the Royal Berkshire hospital (Reading).

Table 2. Mid-point for the step-like increase and magnitude of the increase at MSOA level for residents of the six Berkshire local authorities

Local Authority	Initiation date			Increase in admissions (%)		
	Median	Start	End	Median	Minimum	Maximum
Slough	Oct-11	Apr-11	Apr-12	29%	7%	51%
Windsor, Ascot & Maidenhead	Jan-12	Nov-10	Oct-12	25%	15%	73%
Bracknell Forest	Feb-12	May-11	Dec-12	37%	26%	103%
Reading	Feb-12	Dec-11	Sep-12	41%	25%	68%
West Berkshire	May-12	Apr-10	Jan-13	44%	25%	95%
Wokingham	May-12	Apr-11	Dec-12	51%	14%	119%

Median, Start and End values are for the MSOA components of the larger Local Authority areas.

Across the whole of Berkshire the percentage increase in medical admissions ranges from 10% to 120%, although the most common lies in the range 36% to 48%, and there were two peaks in the initiation dates centered around December 2011 and May 2012. There was no correlation between the initiation date and the percentage increase in admissions (see later for month of year effects). There is no linkage between hospital catchment areas (see footnote to Fig. 1) and the point of initiation or the increase, and this therefore excludes hospital specific factors such as admission thresholds. At MSOA level the timing of the step-like increase appears to follow a random-walk type spread expected from an infectious agent.

Finally in one MSOA (E02003379) lying north-west of the town center of Newbury in West Berkshire, it was difficult to determine an exact initiation date. There was an initial event commencing around March 2010 which had abated by around December 2011. A further event, but of lesser magnitude, commenced around May 2012. If we are dealing with an infectious outbreak it is important to realize that there will be other infectious events occurring in the background arising from the more commonly known viral and bacterial sources, i.e. Norovirus, influenza, respiratory syncytial virus (RSV) and others, which in themselves are also likely to be sometimes highly localized. However the fact that the first event lasted longer than 12 months, is suggestive of the type of event which became very common in late 2011 and throughout 2012 across the whole of Berkshire. A linkage to this early event therefore cannot be excluded.

Various factors with the potential to influence the initiation date or the extent of the increase will now be investigated.

3.3 Effect of Size

Given the range in size of MSOA in Berkshire, median 773 admissions per annum (range 330 – 2,377) before any step-increase, the effect of size on the apparent increase in admissions was tested by taking the average value for the increase in admissions for 19 bands in steps of 100 admissions. The 19 bands were used because equally spaced samples are an assumption for most regression models. As can be seen in Fig. 2, the apparent increase is a function of size, and follows a power-law relationship. The equation given in Fig. 2 was then used to adjust all data to give the equivalent increase at an assumed size of 1,000 (mid-range) admissions per annum. The reasons for a power-law function are discussed later in the section relating to Modifiable Areal Unit Property (MAUP) effects, and relate to the transmission of disease within smaller social networks.

3.4 Effect of Pollution, Temperature and Month-of-Year

Berkshire is a long cigar-shaped county with the M4 motor way running roughly through the middle of the length of the county. Air pollution is known to influence the levels of inflammatory markers and the risk of hospital admission for particular conditions [22]. Given the proximity of most of Berkshire to the M4 motorway, a potential role for air pollution (and temperature) was investigated using monthly averages for particulate matter (PM10), nitrogen dioxide and temperature and comparing these to the percentage increase in admissions observed for each MSOA at the time of the increase. See supplementary material for data on pollution and temperature. Levels of pollutants were highly inversely correlated with temperature, and are highest in the winter months. Neither concentration of the two pollutants nor

temperature could be observed to correlate with initiation date or increase in admissions. The role of proximity to the M4 motorway was also tested and shown to have no discernible effect. Hence while air pollution is known to play a role in health and hospital admission, on this occasion it can be ruled out as a potential cause for the observed events/outbreaks. However, more detailed studies may well show that it plays a contributory role in the extent of the step-like increase.

While temperature did not appear to have an effect, the month of the year (Fig. 3) does appear to have an effect on the average increase in admissions. As can be seen the average increase appears to go through a minimum around October. This indicates a time of year effect rather than temperature, which was previously excluded. The interval July to November also corresponded with the lowest proportion (only 19% compared to 42% based on a random distribution) of MSOA experiencing initiation. This role for month of the year in the initiation date is explored in section 3.7.4.

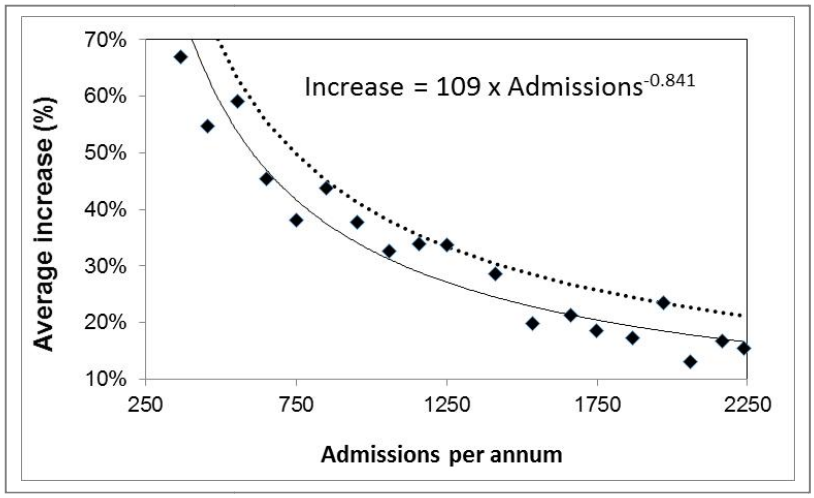

Fig. 2. Effect of size on the apparent increase in admissions due to the step-like changes

Values are the average for each of 19 equally spaced groups in steps of 100 admissions. Admissions are taken before any step-like increase. The trend line is a power-law function using Microsoft Excel curve fit. The dotted line gives the upper 95% Confidence Interval.

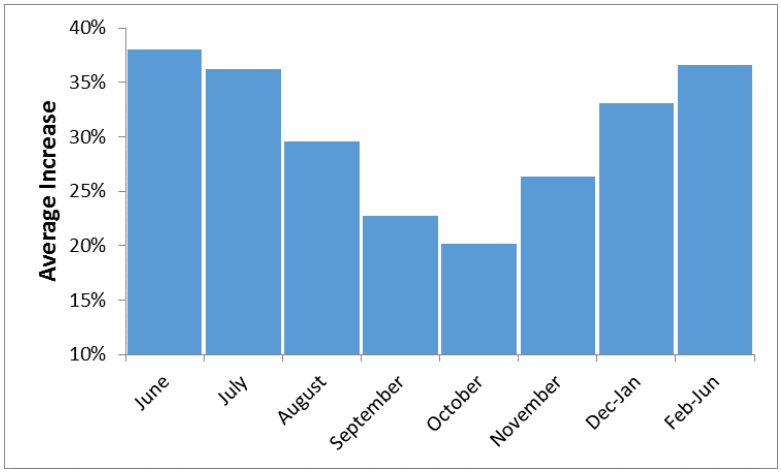

Fig. 3. Role of month of the year for the step-like increase in admissions on average increase in admissions (adjusted for size)

Increase in all MSOA adjusted to the equivalent at 1,000 admissions. Values are the average of the size-adjusted increase seen in each month.

3.5 Age and Gender Standardization

Age and gender specificity is a well-recognized characteristic of many viruses, especially influenza [23] and particular age specificity for those aged 15 to 45 was noted in the 1993 outbreak of this agent [24]. Previous studies have suggested that the step-like increases show unusually high levels of single-year-of-age specificity [5]. Hence the next step was to see if the increase could be calculated using standard 5 year age-bands or single-year-of-age bands. In order to obtain statistically significant numbers for each gender per age band, the before position was taken as January to December 2011, and the after position as January to December 2012. This corresponds to the average point of onset across the whole of Berkshire seen in Fig. 1.

Attempts to predict the increase in admissions in each MSOA using standard five year age bands (by gender), proved to be totally ineffective; however, use of single year of age appeared to be a more successful route. Fig. 4 shows the profile of admissions by age and gender before the outbreak (i.e. during 2011) for the whole of Berkshire. The bulge between 20 and 40 for female admissions are likely to be related to events in early pregnancy presenting to medical assessment units. Fig. 5 shows the relative increase in admissions by year of age using 2012 (during the outbreak) compared to 2011 (before the outbreak). As can be seen there is specific saw-tooth like behavior with age, which explains why the standard 5 year age band approach failed [5].

It is acknowledged that this approach is likely to under-estimate the magnitude of the single-year-of-age effects, since at MSOA level spread across Berkshire occurs over a two year period (Table 1), and the calculated increase is around 3.3% (percentage points) lower than the size adjusted increase for each MSOA (interquartile range -6% to 13%). However using the age-gender estimated admissions after the step-like increase, it is possible to calculate the difference (residual) between the size-adjusted actual to expected admissions, and this difference has then been used to evaluate the contribution from other population factors, i.e. after removing the effects of age and gender. This difference is largely distributed around the average within a band of ± 20% (percentage points). Around 10% of values fall outside this band, and are all high values (clustering either as lower or higher deprivation areas).

In terms of the distribution of MSOA which experienced the greatest increase relative to the expected (gender and age adjusted) increase, these were in the following LAs: Wokingham (n=9), Reading (4), West Berkshire/Bracknell Forest (3), Windsor, Ascot and Maidenhead (1), Slough (0).

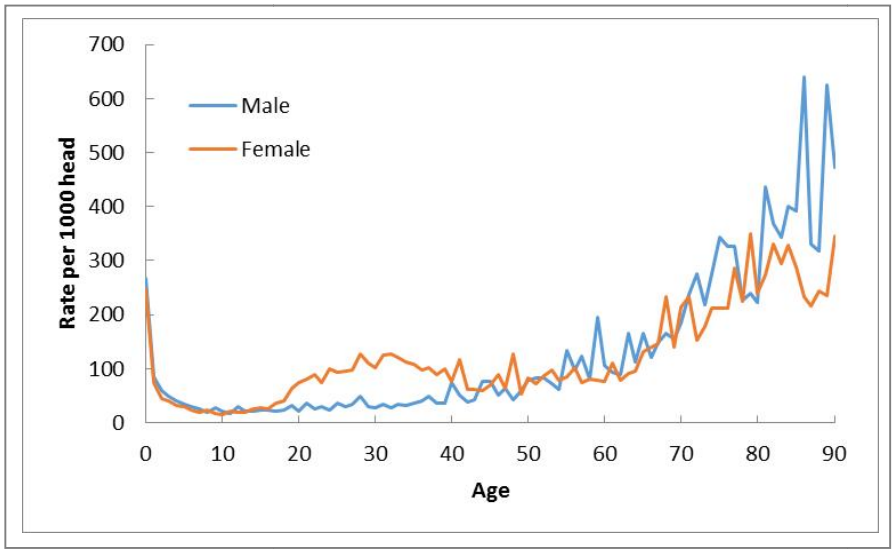

Fig. 4. Admission rate per 1000 population in single year increments before the event (in 2011)

Admissions for each age have been matched against 2011 mid-year census population counts.

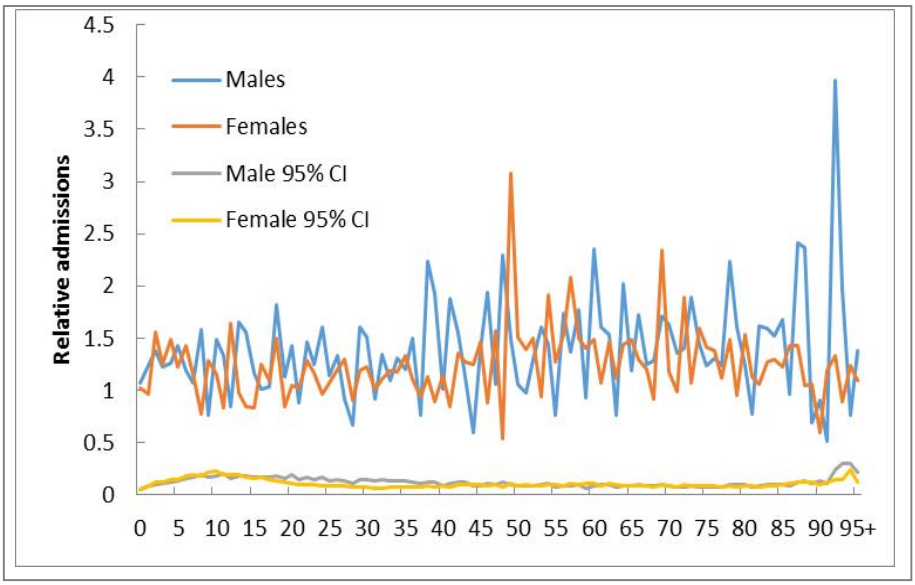

Fig. 5. Relative admissions by single-year-of-age, 2012 versus 2011
The 95% confidence interval was calculated using Poisson statistics

The median value of the size-adjusted difference between the actual and age/gender expected value was 3.3%, indicating that the tendency to underestimate via the age/gender standardized admissions was not large. All values were therefore adjusted down by 3.3% before further analysis.

3.6 Social & Demographic Characteristics

Several likely factors were considered, such as, number of care homes per MSOA (a potential factor highlighted in an earlier study [18]), deprivation levels, and the proportion of the population with a non-white ethnic origin (hence the possible role of genetic variants). In the latter respect, Slough (and a few parts of Reading), has been one of the areas in Berkshire which has attracted successive waves of inward immigration from Pakistan and Bangladesh in the Indian sub-continent. The remainder of the county is largely of white British descent with smaller proportions of Afro-Carribean. On the whole, the white British parts of Berkshire are highly affluent and 60% of MSOA have a deprivation score of less than half the national average.

This section provides somewhat preliminary findings since care homes, deprivation and proportion non-white are all inter-related. Areas with the highest proportion non-white are usually the most deprived, and for these Asian areas it is customary to care for the elderly within the family rather than using care homes. Hence care homes are mainly located in the less densely populated rural and urban areas.

3.6.1 Role of care homes

Work conducted by Public Health England [25] suggested that care homes may be associated with higher deaths during the 2012 outbreak. A high increase in admissions for persons discharged to a care home was suggested in a study on the effect of the 2008 outbreak in North East Essex [18]. However, the use of 'care home' as a discharge destination in the NHS tends to imply that the person was not previously a resident in a care home, but their condition has deteriorated to the point (at discharge) that they now require the use of a care home.

The role of care homes was tested by counting the number of nursing/care homes in each MSOA. Care homes were defined as having nursing support or dealing with those aged 65+ and, as such, most learning disability care homes were therefore excluded. Fig. 6 shows a potential relationship between number of care homes and the increase in admissions relative to that expected from the age-gender mix in each MSOA. As can be seen the increase in admissions is lower as the number of care homes per MSOA increases.

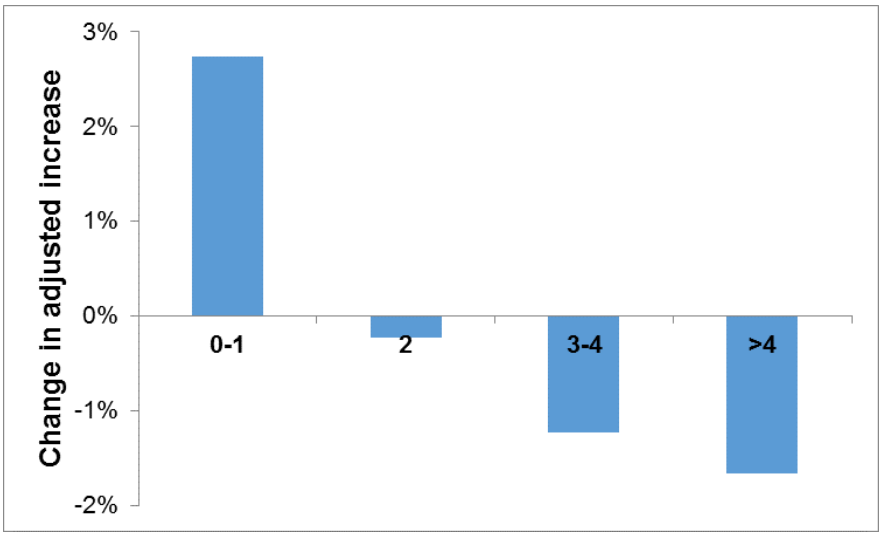

Fig. 6. Potential role of number of care homes in each MSOA to the increase in admissions

Adjusted admissions is the increase adjusted to 1,000 equivalent and calculated is the age-gender expected increase in admissions. Care homes were defined as care homes with nursing or those dealing with those aged 65+. There are a maximum of 9 care homes per MSOA, however MSOA with 4 or more care homes only account for 9% of MSOA and have therefore been aggregated as a single group (only one MSOA each for seven and nine care homes, and only two MSOA contained six care homes)

The curious role for care homes revealed in Fig. 6, is perhaps best explained by the fact that these institutions contain the frailest members of society and will be most susceptible to any type of infectious challenge. Hence they will experience rapid death (confirming the observation of a higher increase in death associated with care homes), which prevents opportunity for multiple episodes of re-admission to hospital. Further study is required which would incorporate the number of beds in each care home and from areas where care homes are more abundant.

3.6.2 Deprivation Score

In the UK a standard deprivation score is available via the Index of Multiple Deprivation (IMD). The IMD is made up from seven domains which could be said to encompass the concept of deprivation in its widest terms, namely; Income Deprivation, Employment Deprivation, Health Deprivation and Disability, Education Skills and Training Deprivation, Barriers to Housing and Services, Living Environment Deprivation, and Crime. These are combined into an overall weighted index of multiple deprivation. IMD has been validated as a measure of health related outcomes [26].

At LSOA level (lowest geography at which IMD is measured), the IMD scores in England ranges from 0.6 (lowest level of multiple deprivations) for one LSOA in Wokingham (Berkshire), through to 86.4 for a single LSOA in Liverpool. The national average for IMD is around 21.7, while the scores for the LA in Berkshire are Wokingham (5.3), West Berkshire (8.2), Windsor, Ascot & Maidenhead (8.5), Bracknell Forest (9.0) which are all well below national average and Reading (19.3) and Slough (22.4) which are close to national average but which contain some pockets of moderately high deprivation. Fig. 7 first explores the role of IMD on the rate of admissions per head before the step-like changes in admissions. As expected the admission rate rises with IMD and probably begins to plateau somewhere above 28 IMD units [27]. Higher admission rates are usually associated with deprivation for the simple reason that persons who are too unwell or otherwise unable to work become dependent on state welfare, and tend to live in state funded accommodation with associated multiple deprivations. As can be seen there is around a 5-fold range in admission rates. Hence more affluent MSOA will, by definition, start at lower levels of admissions and will contain persons who are generally less susceptible to illness, irrespective of age.

Fig. 8 next explores the potential contribution of deprivation to the value of the step-change. To obtain an indication of the likely relationship with IMD, the data was first corrected for the impact of the number of care homes (previous section), and three roughly equally spaced averages were calculated. There are only 13 MSOA with IMD >25 and the average of these (+12%) are shown as the four points with no trend line. The authors own analysis using IMD, has shown that IMD generally reaches a plateau due to the fact that there is a biological limit on the contribution from deprivation. However, in Berkshire there are insufficient MSOA with IMD>25 to reach any definitive conclusions beyond this point.

Further national analysis will be required to see the exact contribution from IMD in more deprived communities such as those in more northern locations such as Middlesborough, Rochdale, Knowsley, Manchester and Liverpool with IMD scores >80. Data was now corrected for the effect of IMD before progressing to the analysis of ethnicity.

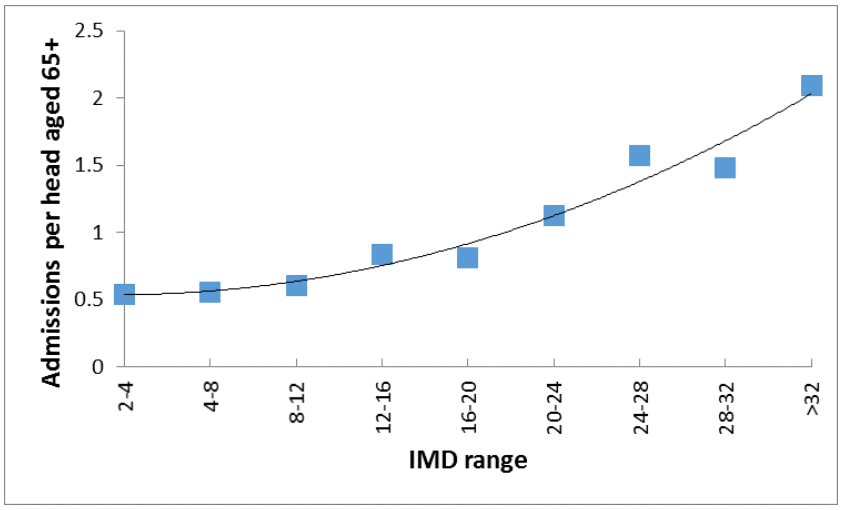

Fig. 7. Admissions prior to the outbreak and deprivation score

Median value in each IMD band. Note that the bulk of the data in Berkshire is for IMD <20. To normalize the admissions as a rate per head total admissions were divided by the number of persons aged 65+ in each MSOA. This approximation was used based on the fact that over 50% of admissions are for those aged 65+

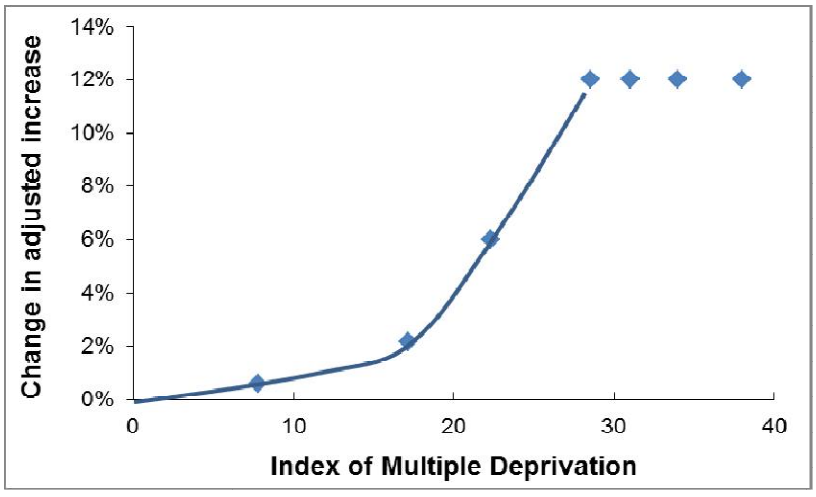

Fig. 8. Effect of IMD on the value of the step-increase

As indicated, Berkshire is a generally highly affluent county, hence the first data point is the average of 73 MSOA, second 10, and third 13, plus 13 for the IMD>25 group.National average IMD is around 22 units

3.6.3 Ethnicity

Census data on ethnicity at MSOA level gives the percentage of the population which is said to be black and minority ethnic (BME). Analysis is made more difficult due to the fact that there are only 13 MSOA with BME >40%. Highest proportions of BME are mainly in MSOA located in Slough, with a couple in Reading, and are predominantly Asian (Indian sub-continent) rather than black.

Predominantly white British populations typically show lower than expected increases in admissions, i.e. 0 to 20% BME (-1%), 0 to 30% (-0.3%), while areas with higher proportions of BME show around 3% higher than expected increase in admissions >30% BME (+3.4%), >40% BME (+3%). Hence ethnicity appears to make only a relatively small contribution, at least within the limitations of the Berkshire data. Further analysis is required using locations with higher proportions of more/less deprived black and Asian residents.

However, as can be seen in Table 2, parts of Slough appeared to experience earlier initiation for the step-like increase, which could be a function of ethnicity. As can be seen in Fig. 9 the proportion of BME does indeed appear to influence the timing of initiation for the step-like increase in medical admissions. Areas of highest BME being among the first to experience the event, and those with exclusively white populations among the last some 12 months later. Reasons for this time cascade will be discussed in more detail in the section relating to month-of-year patterns.

3.7 Discussion and Synthesis of Results

Having established the detail of these infectious-like events, this study has sought to identify population and environmental factors which may be involved in the kinetics and magnitude of the spread. The key features which this study has revealed is the apparent role of ethnicity in the timing and extent of the increase, the role of month of the year, and an apparent role for care homes in modulating the local response. The latter being also noted in NE Essex [18], and in analysis conducted by Public Health England on the 2012 event/outbreak [25].

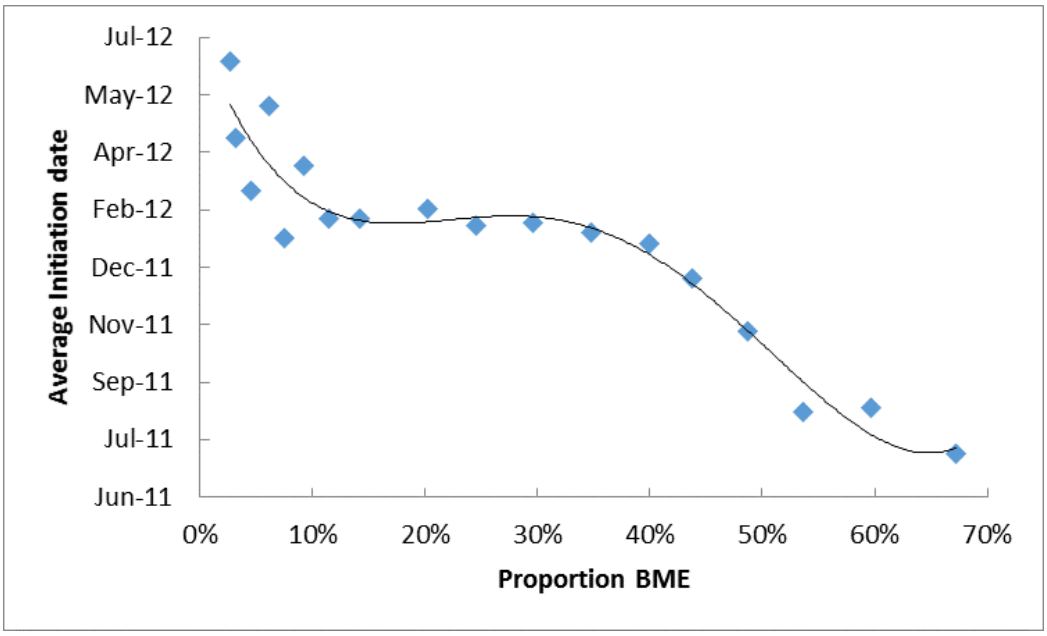

Fig. 9. Effect of proportion black and minority ethnic (BME) on apparent initiation date

Each data point is an average of 10 ranked data (ranked by % BME) selected to lie at every tenth point or at roughly 5% increments in BME. The final data point is the average of the five highest BME locations, while first data point is an average of the five lowest locations

Health care costs in the UK and elsewhere have been characterized by a long-term series of surplus followed by deficit which have been difficult to explain given that such cycles occur in both publicly funded (as in the UK) and private insurance (as in the USA) based health care systems [11,28-30]. Evidence has been recently presented to show that a similar event occurring around November 2008 in the North East Essex area of the East of England led to similar local financial pressures [18], while an event in Wigan occurring around January 2012 led to similar pressures on occupied beds [19], as were experienced in Berkshire during the 2012/13 financial year [20]. Both events are marked by a highly granular infectious-like spread involving large and semi-permanent increases in emergency medical admissions and deaths as per Table 1. This granularity is especially evident in the average for the top 25% of LAs in England versus the average for the bottom 25% of LAs. Preliminary evidence is that those LA's experiencing a low increase in 2012 go on to experience an increase in 2013 [4].

3.7.1 Are large increases feasible?

At MSOA level this study has documented large step-like increases in medical emergency admissions. The median and interquartile ranges are respectively: 39%, 29% - 53% (raw) or 32%, 23% - 43% (adjusted for size). Are such large increases in emergency admissions feasible?

Firstly, similar large percentage increases have been noted at MSOA level following the 2008 outbreak in North East Essex [18], and following the 2012 outbreak in Wigan (near Manchester) [19], i.e. the results are reproducible over time and between different locations.

Secondly, Fig. 4 gives admission rates before the step-like increase which rise up to around 400 per 1,000 population for those aged over 80 years, i.e. in the worst case there are still 600 persons per 1,000 who do not have a hospital admission prior to the outbreak. From national data it is known that the increase in deaths in 2012 was restricted to those aged over 65 years, and that this showed single year of age specificity [5]. In this respect Fig. 5 indicates that the increase in admissions was less age sensitive (in general as an overall trend), but far more single-year-of-age specific, i.e. the net percentage increase is heightened by the far higher numbers of persons aged less than 65 who typically comprise 80% of the population. Fig. 7 also tells us that there is a 5-fold range in admission rates between the least and most deprived groups in Berkshire. It must also be recalled that the admission rate is made up from a range of admissions per person, with higher admissions per person (called re-admission rates) for those with long term conditions [31].

For example, a 2010 study in the USA listed 30 conditions with all-age 30-day readmission rates in excess of 20%, and for the 30 conditions with the most frequent hospital admission, half had readmission rates over 16% giving a 14.5% average readmission rate for these 30 high volume conditions [32]. Readmission rates are also known to increase with age, deprivation, and are higher in those hospitals with a lower in-hospital mortality rate, i.e. patients discharged alive are free to readmit [33]. Hence, there are two potential reservoirs of persons who could contribute to a large rise in admissions, namely, those who have not had any previous admissions (far more prevalent in affluent areas and possibly younger than age 65), and those who by nature of their condition are more susceptible to (repeated) re-admission (far more prevalent in deprived areas) [31].

Given the known relationship between long term conditions such as chronic obstructive pulmonary disease, angina pectoris, acute myocardial infarction, atrial fibrillation, etc and readmission rates [31-32], it is also likely that the few MSOA showing very high increases in admissions probably contained a higher proportion of individuals with specific long term conditions and/or specific social and care problems.

Hence the observed increases, which are only sustained for a period of 12 to 18 months, are feasible and likely to be driven by a cohort of patients with high readmission rates and first time admissions in those aged less than 65 years.

These large increases in admissions are then seemingly reduced as the spatial area increases (as per Fig. 2), such that at the western end of Berkshire the Royal Berkshire hospital, located in Reading, experienced a 16% increase (about half the median increase seen at MSOA level) in occupied beds for the medical group of specialties which commenced in May 2012, which was still ongoing some 17 months later [20]. This increase is roughly the same as previous occurrences of these events documented to occur at this hospital in Mar-93,

Dec-96, Jan-03 and Nov-07 [15,34]. The increase in occupied beds is less than that observed in Fig. 1 due to a relatively larger increase in same day stay admissions via medical assessment units (which do not show as midnight occupancy).

3.7.2 Roles for MAUP

This study has demonstrated that the size of the MSOA (as medical admissions) influences the extent of the apparent step-like increase. The modifiable areal unit problem (MAUP) is a source of statistical bias that can markedly affect the results of hypothesis tests. It affects results when point-based measures of spatial phenomena (e.g. population density) are aggregated into districts. The resulting summed values, e.g. totals, rates or proportions, are influenced by the choice of district boundaries. For example, census data may be aggregated into census enumeration districts, postcode areas, 1 km squares, or any other spatial partition. Hence the "areal units" are "modifiable". In this study MAUP effects are observed when the area studied contains a mixture of effected and not effected clusters, and hence a tendency to the mean. The companion paper to this study gives an example of MAUP by taking the trends in death for the five Berkshire LAs surrounding the Royal Berkshire hospital and blending them by the proportion of patients treated at the hospital [20]. Hence from the viewpoint of the hospital, the net result of the spread is perceived differently to that seen in each LA (as in Fig. 1).

The spread of infectious agents is usually within social networks [35-36] which will be far smaller than the population of an MSOA. Hence the MSOA has become a somewhat arbitrary areal unit. However they are not entirely arbitrary since they are the aggregation of smaller output areas (OA) which are areas of roughly similar social groups and therefore more likely to contain relevant social networks. For example, the North East Essex study noted that each GP surgery (which represents a potential common point for infectious spread throughout the social network comprising the surgery list of patients), typically services one or two MSOA [18]. Hence the larger the MSOA the more likely that points of infectious initiation will be spread over time, and hence the early initiators will tend to elevate the baseline acting to lower the apparent step-increase.

The next lower unit of census geography is a lower super output area (LSOA). LSOAs range from 1,000 to 3,000 population, and MSOAs range from 5,000 to 15,000 population. Therefore an MSOA which is made up from around five LSOA could contain, say, three LSOA with an early response, mixed with two exhibiting a later response, thereby diluting the percentage increase. There were some 21 MSOA (mainly in Windsor, Ascot and Maidenhead) where the expected increase in admissions were less than 95% of the age and gender adjusted expected increase. Given the geography of this LA it is highly likely that such MAUP-based effects were responsible for these lower than expected increases.

3.7.3 Month of year patterns

The general north to south pattern behind the national spread of these events has led to the suggestion that levels of vitamin D may be implicated [1]. Vitamin D is now regarded as a hormone, and vitamin D receptors (VRD) are located in almost all organs and tissues and play a key role in gene expression [37]. Vitamin D deficiency is linked to depression [38], mortality in nursing homes [39], mortality at 30 days after hospital admission for pneumonia and other conditions [40-41], incidence of community acquired blood infections and pneumonia [41-42], increased hospitalization for specific immune-mediated conditions [43], is widespread in pre-dialysis and hemodialysis patients and those attending medical outpatient clinics [44-45] and in those with autoimmune diseases and tuberculosis [46], leads to longer length of stay in intensive care [47], and shows a negative correlation with intact parathyroid hormone [48]. Vitamin D levels alter the levels of immunoglobulins [49], the production of antimicrobial peptides [50] and the immunological route to autoimmunity [51]. Widespread deficiency in institutionalised populations [39,49] is immediately relevant to the observed peak in hospitalizations observed in this study during the winter months and the role of care homes also revealed in this study.

There are several factors within this study which tend to support the proposed role for vitamin D. Firstly analysis of the month of year pattern for the initiation date in Berkshire shows a minimum between July and November. The previously reported outbreak in NE Essex in 2008 [18] had a minimum for initiation in the six months between April to September (25% of MSOAs initiated) with the peak in January/February, while the study in the more northerly LA of

Wigan, near Manchester, following the 2012 outbreak had only 20% of MSOA with an initiation time in the six months March to August with the peak in December/January [19]. While there is clearly some effect due to both location and timing of initial arrival in all cases, the timing for the minimum number of initiation dates seems to largely span the non-winter period. As can be seen in Fig. 10, pooling all three studies gives a clear maximum in December/January with 35% of initiation dates (November to February with 50%), and a clear minimum in July/August with only 8% of initiation dates (June to October with 30%).

Peak vitamin D levels are in the five months June to October with generally lowest levels December through to April and hence highest proportion of the population who are suboptimal [52-53]. Vitamin D deficiency in the UK Asian population (especially women) is known to be highly prevalent and persists all year round due to cultural standards for clothing [54], which may explain the generally earlier initiation dates observed for the higher proportion BME populations in Fig. 9.

In Norway the proportion with vitamin D deficiency is 64% in winter versus 20% in summer [53], while in Scotland it is 54% versus 17% [52]. With respect to this study it must be recalled that over 50% of medical admissions occur in those aged 65+ where vitamin D deficiency in the institutionalised (in Switzerland) can be as high as 66% of subjects [39]. The Scottish study did not demonstrate an appreciable relationship with age, however, it did demonstrate a strong relationship with deprivation where in the most deprived quintile 47% were below 25 nmol/L and 16% below 15 nmol/L [52]. Further study is required to resolve these issues.

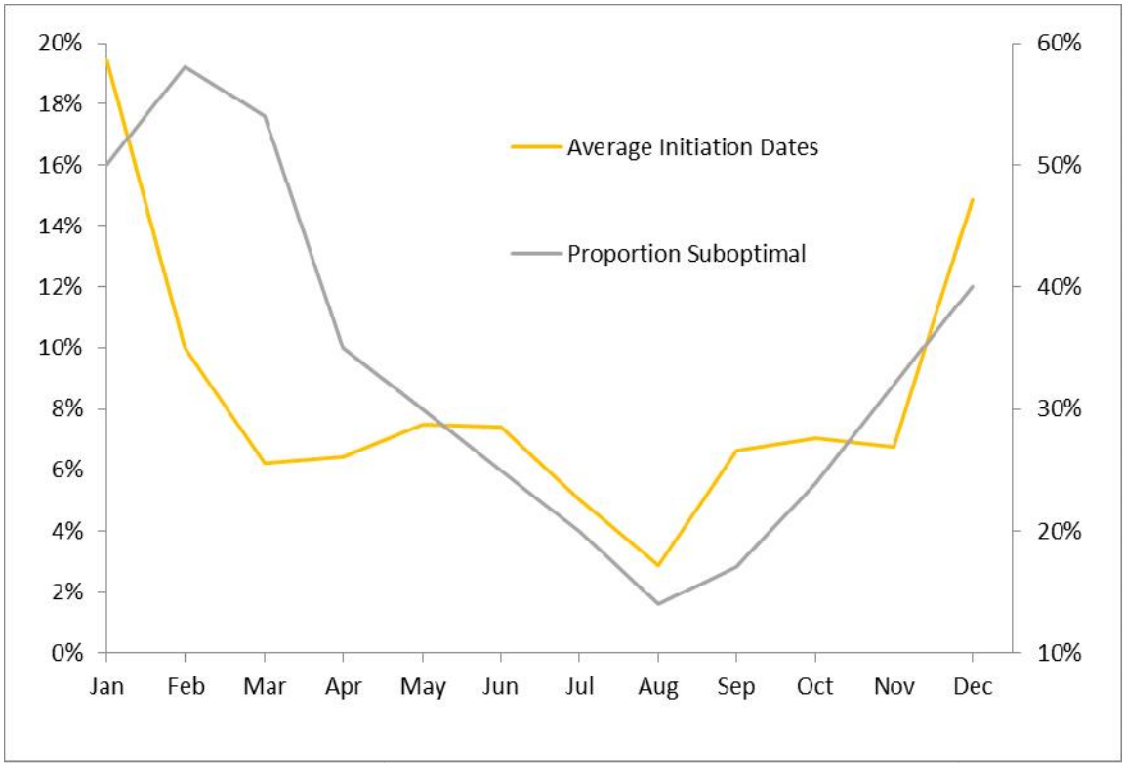

Fig. 10. Proportion of population with suboptimal vitamin D and proportion of initiation dates

Proportion initiation dates (left hand axis) is from the pooled studies in NE Essex, Wigan and Berkshire. Proportion suboptimal (right hand axis) is adapted from Purdon et al. [52] where quarterly values for the proportion of the population who are vitamin D suboptimal have been smoothed to create a month of year profile

3.7.4 Implications to age standardization

With regard to Figs. 4 and 5 it has been widely assumed that age standardization using 5 year age bands represents an adequate level of accuracy and is sufficient for comparison between locations. However this assumption contradicts what is called 'antigenic original sin'. In antigenic original sin, it has been observed that first exposure to a particular strain of an infectious agent primes the immune system such that on the next exposure to a different strain of the same agent the immune system tends to mount a defense to the first rather than the second strain [55]. This can be either beneficial or detrimental depending on the specific characteristics of the two strains. It is for this reason that modern vaccines tend to be multivalent. This is observed to create single-year-of-age saw-tooth patterns in the extent of the response to an outbreak similar to that seen in the pre- and post-outbreak positions in Figs. 7 and 8, and necessitated the use of single year of age standardization across MSOA in attempts to forecast the expected increase for individual MSOA based on their unique age profile.

The pattern of deaths in England and Wales in 2012 has likewise been shown to exhibit very high single-year-of-age specificity [5]. A point of interest regarding Fig. 4 is that the admission rate in the year prior to the event shows evidence for saw tooth behavior in just the same way that deaths in England and Wales do in 2011 [5]. It would appear that these event/outbreaks are of sufficient magnitude to leave a permanent shift in population health characteristics which then appears to be further modified in the next event/outbreak. This strong single-year-of-age behavior has profound implications to the calculation of age standardized rates for medical admission and death, and is likely to be particularly so for the roughly 100 diagnoses/conditions which appear to be most strongly linked to these events [1,56-58].

3.7.5 Potential agents

Based on the pattern of diagnoses associated with the increased admissions, GP referral and the increased deaths [1,7,9,56-58], it has been proposed that the common herpes virus cytomegalovirus (CMV), which has a powerful array of immune modulating strategies, could be a potential candidate, especially among the elderly, who are the subject of immune senescence and the onset of a pro-inflammatory immune state [43]. In 2012/13 in England the age profile for medical admissions is such that 53% were over the age of 65 and 26% over the age of 75, and this provides ample opportunity for such an elderly-focused infectious condition to exist. The issues regarding CMV have been discussed in a number of reviews [1,10-11,56], however other members of the herpes family or another less studied virus, such as from the Mimiviridae, could be implicated. The winter preference for these outbreaks does, however, suggest that a respiratory phase is implicated in these outbreaks, as has been suggested following the NE Essex study [28] and a study of respiratory system deaths during the 2012 outbreak [10].

This supposition is given further weight by the observation that a large step-increase in admissions and deaths for pneumonia occurred during this outbreak at the Royal Berkshire Hospital which is based in Reading [20]. A similar increase in pneumonia has been observed at other hospitals, and results in the hospital being temporarily flagged as having high pneumonia related hospital standardized mortality rate (HSMR) (unpublished studies). The reason that the hospital is temporarily flagged for high HSMR emanates out of the infectious spread across the entire UK. The relative slow nature of the spread creates spatiotemporal anomalies causing the local area to be out of synchrony with a constantly changing national 'average'. With respect to CMV, it is of interest to note that the effect is very much age dependent. In pre-school children CMV is associated with higher levels of respiratory infections [59], while in young adults CMV appears to provide a measure of protection [60], while the situation is reversed in the elderly where CMV interferes with the efficacy of immunization, the ability to clear influenza from the lungs and immune responses to other pathogens [10].

An interesting study regarding vitamin D receptor (VDR) genetic polymorphisms may be helpful in unravelling issues around vitamin D sufficiency, ethnicity, and the exact agent responsible. In this study involving Chinese patients, the recessive f allelic VDR gene Fok1 (hence ff but not FF or Ff) is a risk factor in CMV disease following kidney transplantation [61].

3.7.6 Financial pressures

In a study of the 2008 outbreak in NE Essex, the accompanying financial pressures were highlighted [28]. In response to these pressures,

which were felt across the whole of England, the Department of Health (England) introduced a 70% discount into the Health Resource Group [HRG) tariff for all emergency activity in excess of the 2008/09 out-turn [62]. This has acted to considerably dampen the impact on purchasers (PCTs and now CCGs), however it has had the unfortunate effect of transferring the cost pressures onto the acute sector. It has been recognized that the 70% discount may be causing inequitable cost pressures, especially where the granular nature of these outbreaks coupled with changes in patient flows due to health service configuration changes has unduly affected one location more so than others [63]. In this respect both the financial and bed occupancy impact of these events/outbreaks has been, and continues to be considerable [64-71] – although largely ignored by policy makers.

3.7.7 Nature and speed of spread

Spatiotemporal patterns are commonly observed in all disease outbreaks [72], and this outbreak is no exception. It is clear from the results, that spread across the whole of Berkshire takes 16 months from Oct-11 to Jan-13 (Table 2). Spread of the 2012 outbreak within Wigan occurred between Jan-11 to Jun-12 (18 months) [9] while spread of the 2008 outbreak in NE Essex took 18 months (Apr-08 to Oct-09) [18]. Spread across the whole of the UK (when measured at LA level) appears to take around 26 months [4]. However at small area level (MSOA) the outbreak appears to rapidly take hold in the space of around one or two months. This effect is also observed in Fig. 1 where there is a period of one to two months during which admissions start to rise before the linear part of the line, where it is the onset of the linear increase that marks the start of the large scale step-like increase in admissions for each LA.

Initiation and relative magnitude of the effect against medical admissions has also been confirmed to have a winter peak (which may be related to vitamin D sufficiency). Hence we have a relatively difficult to transmit agent (probably respiratory), which under appropriate conditions, is able to show relatively rapid local spread [10,18,20].

Taking CMV as an example, studies have shown that on average an infected person transmits CMV to two susceptible people [73], and a combination of all of the above is likely to explain the mini-epidemics of CMV illness described in a neighborhood [74], renal transplant unit [75], a laboratory [76], in burns units [77], a neonatal unit [78] and an elderly care ward [79]. The particular nature of the infectious spread observed in small-area studies, indicate that such mini-epidemics may be acting as loci for the bursts of rapid epidemic-like local spread which then nest-up to give the trends observed at MSOA and LA level. The mini-epidemic in a neighborhood was noted to accompany flu-like symptoms [74], and an unseasonal peak in flu-like symptoms was noted to occur around the time of the 1993 outbreak [80].

Spatial proximity is well recognized as a risk in viral transmission [81], and coughing, sneezing or shaking of bed linen all place infectious agents into air currents which facilitate transmission [82]. In patients with unrecognized CMV disease, respiratory symptoms occur in 28% visiting their GP and 39% for those who are hospitalized [83]. The lungs are a recognized major reservoir for CMV [84], which can be detected in the air surrounding those with CMV-respiratory infections and those with no apparent symptoms [85].

The final evidence implicating CMV is the fact that this virus has a large effect against all-cause mortality, see reviews [10,11,56], and these outbreaks (with associated increases in mortality), are proposed to be part of the expression of the heightened mortality rate observed in these large population studies.

3.7.8 Policy implications

In England, Primary Care Organizations are at the forefront of endeavors to implement cost saving initiatives as directed by government policy. Previous studies have highlighted that these outbreaks tend to increase admissions with non-specific diagnoses typically found in the ICD Chapter R which is devoted to signs and symptoms [1,14,21]. It has been suggested that this is consistent with a new disease entity where there is no current definition of the disease or range of tests to identify the particular agent. Hence diagnostic uncertainty is a natural outcome [1]. Indeed if the agent acts via modification of immune balance, then a complex range of outcomes is also likely depending on the inflammatory/autoimmune sensitivity of each condition [1,7-11,15,56]. Up to the present this diagnostic ambiguity has been interpreted to mean that the (cumulative) unexpected increase in admissions due to these outbreaks [62] must

therefore be either unnecessary, avoidable or preventable. Obviously until the disease is defined it is impossible to say whether unnecessary, avoidable or preventable actually applies.

Current government policy in England is toward the integration of health and social care in order to provide a patient centered approach using case managers coupled with patient empowerment [86-87]. In patient empowerment the patient is taught how to better manage their specific condition(s) such as diabetes, cardiovascular disease, etc. Such approaches can indeed be highly successful [86-87], however, without the impact of an infectious agent being characterized, the patient and their wider care team will be equally perplexed when the patient falls ill.

Secondly, while integrated care/case management may well lead to a step-like reduction in total costs, a time series of infectious outbreaks with the semi-permanent effects apparently associated with this agent will (eventually) overwhelm the cost savings. The appropriate response is to identify the infectious agent and implement the necessary public health measures. To emphasize, while integrated care and case management are entirely appropriate interventions for ageing western populations with co-morbidities, they are entirely inappropriate to preventing and treating the spread of an infectious agent.

Indeed there are huge implications to end-of-life care (Table 1) since deaths peak during these outbreaks.

Lastly, current government policy (in England) is to reduce costs by outsourcing aspects of care to private organizations who will (presumably) implement cost saving initiatives in order to both improve care and also create a profit margin. Once again, where appropriate, such schemes will result in a one-off step-like reduction in costs which will be eroded by the next outbreak of this agent. Such private organizations may then accuse the government of not informing them of the action of this infectious agent, and either cut costs by reducing care or demand a higher price. Indeed the financial impact of these outbreaks has been well characterized [28-30,66,71] but has not been acknowledged by the Department of Health and associated government agencies.

Studies suggesting the role of a previously uncharacterized infectious agent have been steadily accumulating since the first studies published over six years ago in 2009 [65-66,88-89]. Could this be a case where early adoption of a new discovery has been hindered by government policy taking precedence over a scientific reality, which appeared to contradict policy? Such selective use of the available evidence has been called ‘policy based evidence’ as opposed to ‘evidence based policy’ [90]. It is clear that urgent studies are needed to avoid implementing policies in the incorrect hope that they will address the ‘problem’.

3.7.9 Limitations and further studies

As with any population-based study the ecological fallacy implies that this study does not predict the behavior of individuals, nor does it imply that the apparent relationships with demographic characteristics will apply to all populations. In particular Fig. 9, effect of proportion BME on average initiation date could be subject to the ecological fallacy and therefore requires further validation.

The limitations of the Berkshire data have been highlighted throughout earlier sections. This study has, however, demonstrated consistent behavior over time, i.e. the 2008 outbreak versus the 2012 outbreak, [18-19] and consistency between widely different locations, i.e. Berkshire, Wigan and North East Essex [18-19]. In addition, it has attempted to show the potential effect of relevant demographic variables upon infectious spread between spatial units, and established that whatever is happening conforms to expected norms for a type of infectious spread.

It is therefore suggested that further studies use LSOA as the geographic unit, which although suffering from smaller numbers of admissions and hence the possibility of higher random effects, will, however, show far higher discrimination for deprivation (IMD), household overcrowding, %BME, age and gender profiles and the exact location of nursing homes. With over 30,000 LSOA in England, the use of LSOA is also more in keeping with the concept that infectious spread is via urban social networks [35-36] which are far more likely to be concentrated in the smaller LSOA geography. The percentage increase should therefore be more focused, and this should outweigh the limitations of fewer admissions. Population density is also more easily estimated at LSOA

level (using the constituent OAs), and in this respect ambulance call-out rates are known to show highly non-linear trends with population density [91].

LSOAs with similar initiation dates and social characteristics can then be aggregated to once again gain the benefit of size. On this basis it remains to be seen how much the outcome of average time of initiation (Fig. 9) is an outcome of MAUP effects especially in those MSOA with multiple larger population centers. The results at LA level shown in Fig. 1 are to be seen in this light. Likewise the calculation of expected increase in admissions based on gender and single year of age rates has probably underestimated the exact effect of age due to these MAUP related effects.

The results presented in Table 2 are highly apposite regarding the funding formula used to distribute resources to NHS purchasers, namely, that the outcome of these outbreaks along with the powerful single-year-of-age effects, has not in any way been incorporated in the design of the funding formula, and the obvious granularity of effect, will create disproportionate (unfair) financial pressures between primary care organizations [64].

Finally, we need to address the issue as to whether this and other studies are sufficient to 'prove' causation. In this respect Howick et al. [92] have modified the Bradford Hill's 'guidelines for causation' to give the following broad categories:

1. *Direct evidence* from studies (randomized or non-randomized) that a probabilistic association between intervention and outcome is causal and not spurious;
2. *Mechanistic evidence* for the alleged causal process that connects the intervention and the outcome;
3. *Parallel evidence* that supports the causal hypothesis suggested in a study, with related studies that have similar results.

Within these three broad categories it would seem that the case for a new type of infectious outbreak has been established but awaits final proof of the infectious agent.

4. CONCLUSION

Evidence has been presented for a granular and spatial spread of an infectious-like agent across Berkshire, leading to dramatic increases in emergency medical admissions, which endure for 12 to 18 months before beginning to abate. A persistent infectious agent is implicated which has multiple strains. Maximum spreadand effect appear to occur during the winter months and the likely involvement of a respiratory phase of infection can be deduced. The most deprived areas, which already have very high medical admission rates prior to the outbreak, show the highest response. Ethnicity may be implicated, but further research is required to disentangle the effects of ethnicity, deprivation, household crowding and population density.

A companion paper to this study details the effect of this outbreak upon the operational pressures at the Royal Berkshire hospital in the western part of Berkshire, and gives evidence for time-based cascades in admissions and deaths which appear to arise out of immune-based changes in the balance between inflammatory and autoimmune pathways in different diseases [20]. Urgent research is required to determine the exact infectious agent responsible for these outbreaks, and potential immunological/ biochemical tests to enable diagnosis.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not required. No patient identifiable data was used in this study. Only aggregated data extracts were provided for analysis. Permission from the Director of Public Health (Berkshire) was obtained to conduct this epidemiological study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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