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Infectious-like spread of an agent leading to increased medical hospital admission in the North East Essex area of the East of England

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Abstract

This work documents the spread of a new type of infectious-like outbreak leading to a step-increase in emergency medical admissions. It employs a running 12 month sum of emergency medical admissions to detect step-like changes in admissions from small areas, namely Mid Super Output Area (MSOA) geographical areas and from GP practice enrolled patients. A general 25% step-like increase in emergency medical admissions occurred around November of 2008 in North East Essex due to gradual spatial spread of an infectious-like agent. Earliest incidence seems to be around August 2007 at a GP surgery in the Castle ward of Colchester leading to a 21% increase in medical admissions. The next major incidence appears to be around January of 2008 at a GP Surgery in the Shrub End ward of Colchester with a 32% increase in admissions. Sporadic occurrences can be seen in April and May of 2008 in four small areas with 21% to 65% increases in medical admissions. The major outbreak occurred in October, November and December of 2008, hence the apparent November 2008 date seen in the aggregated data for the entire area. Further sporadic spread continues through to October 2009. Several small areas appear to have escaped the outbreak, notably a rural GP practice in the village of Lawford and an area of Colchester dominated by student bed sits. More deprived elderly communities represent the social groups most affected. The outbreak shows strong age dependence which is reminiscent of what is termed 'original antigenic sin', *i.e.* age at first exposure to a strain of an infectious agent determines the quality of the immune response to later exposure to different strains of the same agent. There is evidence to suggest that residents of nursing homes are affected earlier and more strongly than others while those who die in hospital show only a modest increase, *i.e.* the infection generally leads to sustained poor health rather than death. Analysis of the primary diagnoses for those admitted to hospital strongly suggests that the agent may be the common herpes virus cytomegalovirus and this is consistent with the apparent time cascade in disease which emanates out of each outbreak. Other explanations may be possible. These findings have profound public health implications regarding the infectious origin of disease, to the funding formula used to distribute health care funds both in the UK and elsewhere and to the interpretation of age-standardized admission rates for medical admissions.

Abbreviations: CMV: Cytomegalovirus; CRP: C-Reactive Protein; DH: Department of Health; GP: General Practitioner; HRG: Healthcare Resource Group; LA: Local Authority; LSOA: Lower Super Output Area; MAU: Medical Assessment Unit; MSOA: Mid Super Output Area; OA: Output Area; OAC: Output Area Classification; ONS: Office of National Statistics; PCT: Primary Care Trust (a PCT is a PCO); PCO: Primary Care Organisation; UK: United Kingdom; USA: United States of America

Introduction

A series of long-term cycles appear to characterize the behavior of emergency medical admissions across the UK and elsewhere in the Western world [1-3]. Each cycle is composed of local infectious-like outbreaks which nest up over wider areas to give the appearance of a cycle at larger regional or national level. Each outbreak displays age and gender specific effects [4-7], and moves across the whole of the UK over a period of one to two years and are associated with sudden and unexpected increases in deaths, emergency department attendances and health care costs [3,4,8-10] sufficient to create a long-term cycle in NHS surplus and deficit [11,12] and also appear to initiate a parallel cycle in the gender ratio at birth [13].

There are two suggested reasons for these infectious-like events. The first suggests that the events are merely the result of acute hospitals changing their threshold to admission [14], while the second suggests that this is a genuine infectious outbreak of a relatively slow to transmit persistent virus [1-12]. It does need to be pointed out that the first hypothesis cannot explain the increase in deaths or the cycle in the gender ratio at birth, however, it is possible to test these two hypotheses using the geographic area of a single hospital where the flow of patients is restricted to the hospital due to natural barriers to travel.

Such a situation exists in North East Essex, part of the larger East of England region. The population reside in three seaside townships of Harwich, Frinton-on-sea and Clacton-on-sea and in Colchester, a larger inland town which contains the main acute hospital. All roads converge on Colchester due natural barriers to travel provided by the estuary of the Clone to the south, estuary of the Stour to the north and the North Sea to the east. Surrounding countryside is largely dedicated to agriculture with a scattering of small villages and hamlets. Hence

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we have an ideal location in which to evaluate if hospital thresholds to admission or an infectious spread account for an unexpected increase in medical admissions which commenced in 2007 across the UK [3,7-9].

In England all census data and resulting social classification of the population commences at the level of an output area (OA) containing roughly 300 head of population. Each OA is assigned to an output area classification (OAC) which consists of 7 supergroups, 21 groups, and 52 subgroups which area social classification constructed from 41 census variables. Each OA then nests up to a lower super output area (LSOA), to mid super output area (MSOA), to Parish, to Ward, to Local Authority and then to government or Health Service regions. Primary Care Organisations (PCOs) usually have a geography matching one or two Local Authority areas. Each Local Authority typically contains more than 100,000 head of population and in this respect NE Essex comprises two local authority areas of Colchester (population 170,000) and Tendring (150,000), serviced by 44 General Practitioner (GP) practices. Only 54% of the population lives in an urban area compared to 73% for England, and life expectancy at birth is only one year lower than the England average due to some pockets of high deprivation in some of the sea-side towns [15].

This study goes beyond the previous large area studies [1,3-7,10], and moves the analysis of these events down to the small area of an English MSOA (roughly 5,000 head of population) to demonstrate small area spread consistent with an infectious event.

Methods

Data for emergency (non-elective) admissions was supplied by the former North East Essex Primary Care Trust (PCT) and covers monthly admissions for the residents of NE Essex over the period April 2005 to May 2010. Data did not contain patient identifiable features such as name, address, and postcode, date of birth or NHS number. Emergency (non-elective) admissions to the medical group of specialties were analyzed as a single cluster and include general medicine (42%), elderly medicine (33%), cardiology (9%), thoracic medicine (6%), gastroenterology (4%), oncology (3%), nephrology (1%) and other smaller medical specialties. Monthly trends for adult emergency medical admissions with a length of stay of one night or more were constructed and analyzed in a number of ways. In the first, all admissions at OA level were assigned into 17 concentric rings at 1 km intervals centered on the acute hospital in Colchester. The straight line distance of the population centroid of each OA to the hospital was calculated and this distance was used to allocate the admissions into the concentric rings. The aggregated data for each ring was available for analysis in this study. In the second method the admission trends in the largest MSOA were studied. In the third, all admissions were aggregated at the level of GP practice and trends for the largest practices were studied. Lastly data at OA level was aggregated to one of the 52 sub-groups in the Office of National Statistics (ONS) Output area classification (OAC) which are social groupings based on census data. The 2001 OA's and associated OAC's were obtained from the ONS. The OA code was then deleted and only the larger OAC aggregates were studied. None of the four methods involved patient identifiable aggregates, as discussed above, and the geographic units generally contained more than 100 admissions per annum to the wider medical group of specialties. Analysis of aggregates with less than 100 admissions is also not desirable from a statistical point of view since Poisson variation can act as a confounding factor in the analysis.

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 = $2.7 \times n^{-0.5}$.

One Figure in the results section presents actual monthly data which has been adjusted for the number of day per month and seasonal behavior. The seasonal (monthly) adjustment factors were calculated using the Solver function in Microsoft Excel to minimize the sum of the absolute difference between one month and the next in the adjusted monthly values.

Results

Trends were studied using running twelve month sums. Such a running twelve month sum avoids the need for complex analysis due to the seasonal nature of medical admissions. If demographic trends were the sole source of the admission behavior over time then such a running sum would generate a straight line whose slope would reflect approximately 1.0% to 1.5% per annum growth due to demographic shifts or what is known as the ageing population. In a running sum a step-change is transformed into a ramp. The base of the ramp marks the onset of the step-change and the ramp is only sustained if the step-change endures for 12 or more months.

Figure 1 presents the unusual situation confronted by the NE Essex PCT. Medical admissions had declined to a minimum by around March 2007, *i.e.* 12 months prior to March 2008 in the running sum trend, and continued at this low rate through to around November 2008 at which point there was a large and totally unanticipated 25% step increase resulting in serious financial pressure and a large ensuing deficit [16,17]. As can be seen there are no significant changes in any other specialty group other than general and elderly medicine and this argues against a hospital-wide reduction in the admission threshold or even a reduction in the threshold for admission through the emergency department. While the boundary between general and elderly medicine is somewhat fluid the average age is higher in elderly medicine. Note the slightly different time profiles between the two, especially the earlier larger step-down in elderly medicine. To give a statistical context to each of the trend lines the maximum possible Poisson-based variation is as follows (99.9% CI as a number and percentage): Trauma (±116, ±8%), All Others (±132, ±7%), Pediatrics (±141, ±7%), Surgery (±172, ±6%), General Medicine (±342, ±3%), Geriatric Medicine (±269, ±4%). While these statistical fluctuations can explain some of the small undulations seen in the non-medical specialty trends they are totally unable to explain the behavior in General and Elderly Medicine.

Figure 2 examines the situation for the trends observed in the concentric rings surrounding the acute site in Colchester. In this Figure trends are relative to the minimum 12 month total in each ring. Exemplar trends have been selected, namely, lowest, middle and highest magnitude for the step change and earliest and latest point for the start of the step change. As can be seen there are a range of dates covering the initiation of the step-change and for the magnitude of the step-change. Table 1 presents further details for each of the concentric rings including age, proportion female, number of admissions, the initiation date and details of the largest MSOA contained within the

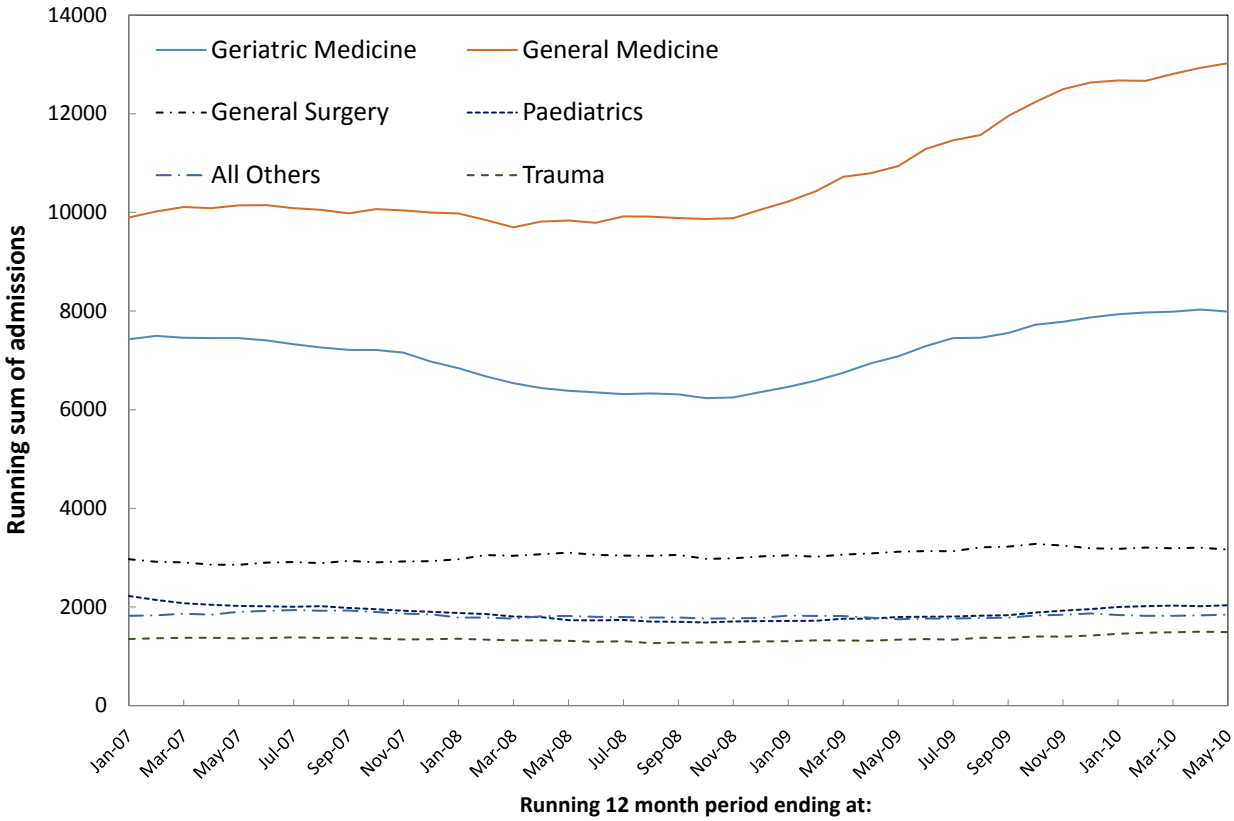


Figure 1. Running 12 month total trends in emergency admissions in North East Essex by specialty of admission.

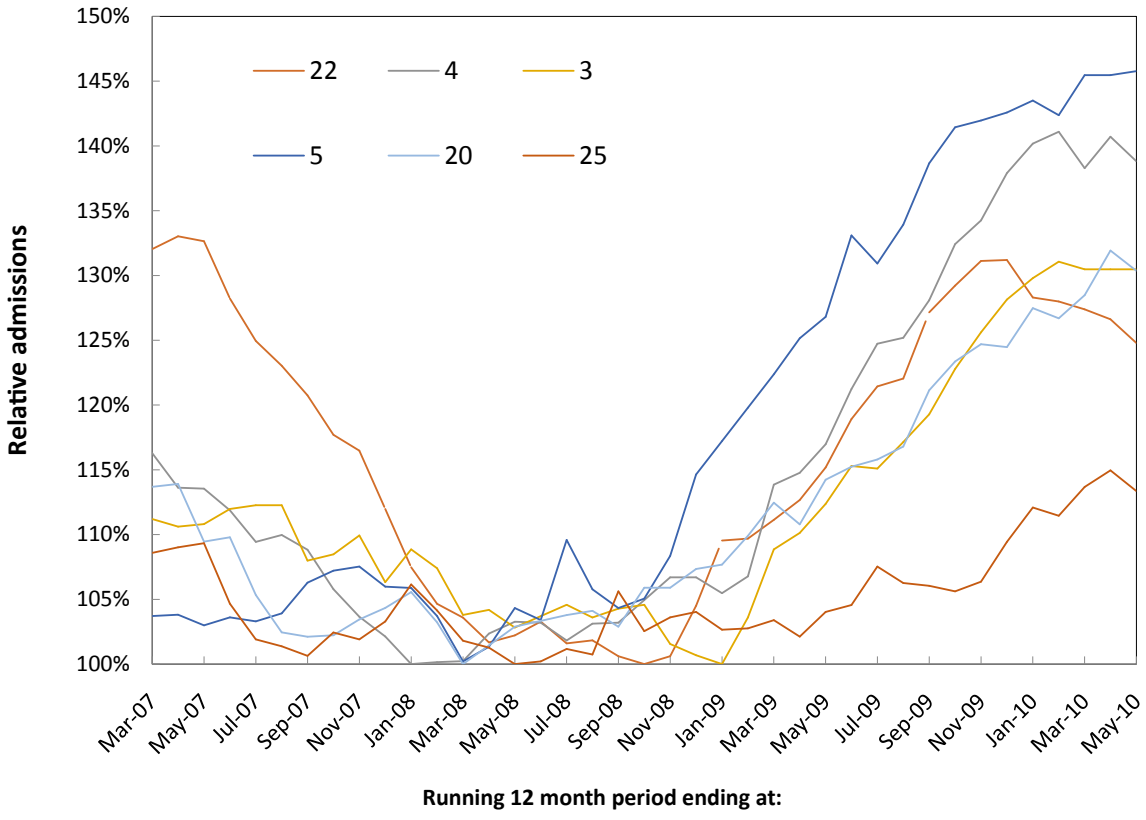


Figure 2.Step-like increase in admissions within the six rings with highest admissions.

Table 1. Characteristics of 1 km concentric rings surrounding Colchester hospital, including population age, admissions, step-like increase and the initiation date, and the largest MSOA in the ring (including the proportion of admissions attributable to the largest MSOA).

Ring (km)	Age			Female (%)	Admissions			Initiation Date	Largest MSOA in ring	
	Average	STDEV	Mode		Minimum	Increase	97.5% CI		Largest MSOA	Proportion
14	72.3	23.3%	82	49.8%	598	35%	11%	Jun-08	Tendring 011B	22%
11	69.7	25.4%	78	49.8%	207	39%	22%	Jul-08	Tendring 009D	38%
15	72.5	23.0%	85	50.1%	533	18%	12%	Jul-08	Colchester 020A	18%
19	70.7	22.5%	77	49.7%	347	37%	17%	Aug-08	Tendring 007C	38%
5	67.9	28.4%	83	50.6%	970	35%	6%	Oct-08	Colchester 012C	12%
20	70.4	24.5%	76	50.2%	899	18%	7%	Oct-08	Tendring 018B	17%
2	66.8	29.7%	85	51.5%	1,020	30%	8%	Nov-08	Colchester 007A	11%
7	70.1	25.3%	87	49.7%	389	42%	16%	Nov-08	Tendring 005D	19%
22	74.0	23.3%	85	51.9%	1,311	30%	7%	Nov-08	Tendring 017D	16%
6	66.7	30.3%	81	49.8%	374	40%	16%	Dec-08	Colchester 012E	18%
8	73.3	23.4%	88	51.5%	268	52%	19%	Dec-08	Brabergh 009D	32%
17	71.8	24.1%	79	51.4%	89	76%	32%	Dec-08	Tendring 018E	83%
21	70.1	23.7%	74	50.5%	1,857	30%	6%	Dec-08	Tendring 018A	10%
26	74.5	21.2%	85	51.2%	767	25%	9%	Dec-08	Tendring 008H	30%
1	64.5	31.3%	87	50.3%	356	50%	16%	Jan-09	Colchester 004B	30%
12	73.2	22.7%	89	52.9%	102	16%	30%	Jan-09	Tendring 003F	93%
18	72.3	21.8%	71	50.8%	102	25%	30%	Jan-09	Tendring 018D	100%
3	67.1	28.8%	85	51.0%	1,027	30%	8%	Feb-09	Colchester 008D	10%
10	67.4	25.5%	88	49.4%	189	31%	23%	Feb-09	Colchester 019B	29%
23	74.4	20.8%	85	49.7%	559	27%	12%	Feb-09	Tendring 012B	24%
4	67.4	29.5%	82	50.9%	1,314	30%	7%	Feb-09	Colchester 008A	7%
9	68.4	26.1%	85	50.4%	184	34%	23%	Mar-09	Tendring 009A	49%
13	70.8	24.6%	80	49.8%	441	31%	14%	Mar-09	Tendring 009C	27%
24	73.4	20.6%	85	51.1%	549	48%	12%	Mar-09	Tendring 012A	34%
16	70.7	22.3%	78	49.9%	301	54%	18%	Apr-09	Tendring 011E	34%
25	74.9	20.8%	85	51.0%	943	13%	7%	Apr-09	Tendring 006B	14%
27+	67.6	29.2%	78	49.5%	307	40%	18%	Jun-09	Tendring 006C	35%

*The three rings where a single MSOA comprises the bulk of the admissions have been shaded.

ring and the proportion of total admissions in the ring which occur in the largest MSOA. Note the wide range in the initiation date from June 2008 through to June 2009 and the variable extent of the step-change ranging from +13% through to +76%. Note that all step-increases in this table are statistically significant except for rings 12 and 18 which only contain around 100 admissions.

To gain further evidence for an infectious-like spread Table 2 summarizes the details for the largest MSOA aggregates. Note that in these smaller geographical units the initiation dates show a wider spread from April 2008 to October 2009 while the increase ranges from +16% to +70%. In this table, the 97.5% confidence interval (CI) has been calculated from Poisson variation and represents the maximum possible contribution from Poisson variation to the step-change. Hence for the first MSOA (E02004517) in Table 2 the measured 65% step-increase has a maximum possible 15% increase which could be due to chance, *i.e.* something higher than a 50% step-increase can be guaranteed to be due to the infectious agent, on the other hand the real step change could be as high as 80%. Even the smallest MSOA (Colchester 010A) with only 131 admissions in the twelve months prior to the step-increase has a change well beyond the 97.5% CI for Poisson variation.

Since GP practices service their patients from the close geographic vicinity Table 3 investigates the impact at GP practice level. An even wider spread in the initiation date is detected using this method from August 2007 through to June 2009 with the usual wide range in magnitude of the step change. The point of great interest is a single practice in the Lawford area which experiences no apparent increase in medical admissions over the period studied. Lawford is a rural village in the Tendring LA some 15 km to the northeast of Colchester, and is situated in an otherwise sparsely populated area.

Figure 3 shows the actual monthly medical group admissions (rather than a running sum) in the concentric rings with onset clustered around October, November and December 2008. This data has been

Table 2. Characteristics for the largest MSO Aincluding minimum admissions, value of the step-like increase and apparent initiation date.

MSOA	Name	Minimum Admissions	Step-like Increase	97.5% CI	Apparent Initiation
E02004517	Colchester 012E	399	65%	15%	Apr-08
E02004589	Tendring 017A	710	21%	9%	May-08
E02004583	Tendring 011B	620	33%	11%	May-08
E02004579	Tendring 007B	481	22%	13%	Jun-08
E02004525	Colchester 020E	434	24%	14%	Jun-08
E02004520	Colchester 015E	333	45%	17%	Jun-08
E02004513	Colchester 008D	527	27%	12%	Aug-08
E02004586	Tendring 014B	776	23%	9%	Sep-08
E02004510	Colchester 005B	258	33%	20%	Sep-08
E02004515	Colchester 010A	141	70%	26%	Sep-08
E02004511	Colchester 006D	619	21%	11%	Oct-08
E02004573	Tendring 001B	381	40%	16%	Oct-08
E02004524	Colchester 019B	335	21%	17%	Oct-08
All MSOA	***NE Essex Total***	***21,123***	***24%***	***2%***	***Nov-08***
E02004590	Tendring 018B	845	51%	8%	Nov-08
E02004588	Tendring 016A	759	20%	9%	Nov-08
E02004582	Tendring 010A	684	23%	10%	Nov-08
E02004521	Colchester 016B	489	32%	13%	Nov-08
E02004516	Colchester 011C	345	42%	17%	Nov-08
E02004507	Colchester 002B	324	34%	17%	Nov-08
E02004584	Tendring 012A	713	31%	11%	Dec-08
E02004575	Tendring 003A	560	23%	12%	Dec-08
E02004519	Colchester 014B	451	24%	14%	Dec-08
E02004509	Colchester 004C	298	44%	18%	Dec-08
E02004508	Colchester 003A	238	30%	21%	Dec-08
E02004587	Tendring 015A	654	35%	10%	Jan-09
E02004585	Tendring 013A	658	32%	10%	Jan-09
E02004581	Tendring 009A	481	30%	13%	Jan-09
E02004526	Colchester 021B	453	22%	14%	Jan-09
E02004574	Tendring 002A	388	50%	16%	Jan-09
E02004514	Colchester 009C	307	28%	18%	Jan-09
E02004506	Colchester 001B	279	35%	19%	Jan-09
E02004576	Tendring 004A	533	25%	12%	Feb-09
E02004512	Colchester 007D	520	23%	13%	Feb-09
E02004523	Colchester 018E	419	48%	15%	Feb-09
E02004522	Colchester 017A	336	30%	17%	Mar-09
E02006235	Babergh 009A	169	54%	24%	Mar-09
E02004578	Tendring 006B	724	13%	11%	May-09
E02004577	Tendring 005A	239	18%	21%	May-09
E02004518	Colchester 013A	265	23%	20%	May-09
E02004580	Tendring 008A	1,202	16%	9%	Oct-09

Table 3. Characteristics of the step-like increases observed for the largest GP practices.

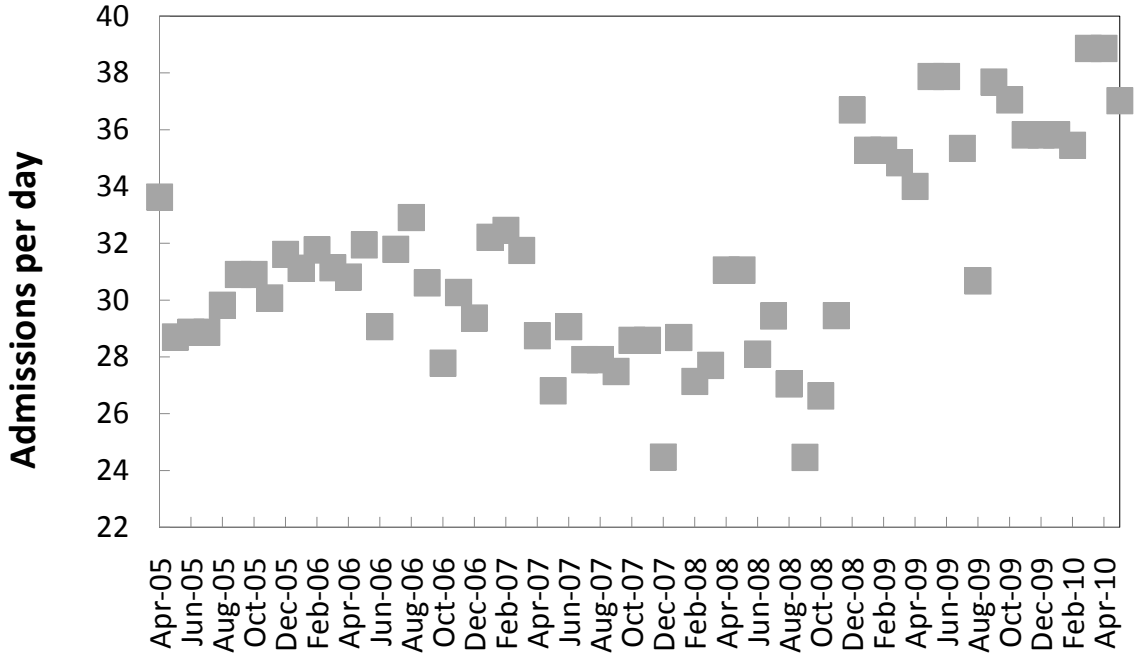
Practice Postcode	Initiation	Minimum Admissions	Increase	97.5% CI	Name and Location	Ward
CO1 2QS	Aug-07	318	21%	18%	Castle Gardens Medical Centre, Colchester	Castle
CO3 4RY	Jan-08	284	32%	19%	Shrub End Surgery, Colchester	Shrub End
CO3 0PZ	May-08	199	30%	23%	Winstree Road Medical Practice, Colchester	Stanway
CO5 0TJ	Jun-08	484	16%	13%	Tiptree Medical Centre, Colchester	Tiptree
CO12 3RS	Aug-08	264	31%	20%	Fronks Road, Harwich	Harwich East Central
CO15 4DA	Sep-08	765	21%	9%	Great Clackton Surgery, Clackton	St Marys
CO15 1DA	Oct-08	982	43%	6%	St James Surgery, St Osyth, nrClackton	St James
CO2 8QY	Oct-08	484	31%	13%	Mersea Road Surgery, Colchester	Berechurch
CO1 2RW	Oct-08	365	46%	16%	East Hill Surgery, Colchester	Castle
CO4 3GW	Oct-08	189	19%	23%	Hawthorn Surgery, Colchester	St Andrews
CO15 2NB	Nov-08	453	76%	14%	Green Elms, Clackton	Golf Green
CO15 4TN	Nov-08	207	73%	22%	Crusader, Clackton	Burrsville
CO7 7LD	Nov-08	179	32%	24%	Ardleigh Surgery, Colchester	Ardleigh& Little Bromley
CO3 3HZ	Dec-08	569	25%	12%	Creffield Road Surgery, Colchester	Christchurch
CO4 3HS	Dec-08	475	33%	13%	Parsons Heath Surgery, Colchester	St Anne's
CO5 7HP	Dec-08	194	51%	23%	Rowhedge Surgery, Colchester	East Donyland
CO7 0DT	Jan-09	559	50%	12%	Colne Medical Centre, Brightlingsea	Brightlingsea
CO12 4EX	Jan-09	490	67%	13%	MMC - Alldrick, Harwich	Harwich West Central
CO15 3AU	Jan-09	453	31%	14%	Old Road, Clackton	Pier
CO15 5UW	Jan-09	472	64%	14%	Frinton Road, Clackton	St Bartholomews
CO5 8RA	Jan-09	366	22%	16%	Mersea Island Surgery, Mersea Island	West Mersea
CO7 9PP	Jan-09	297	38%	18%	Wivenhoe Surgery, Colchester	Wivenhoe Quay
CO4 5LE	Jan-09	244	72%	20%	Mill Road Surgery, Colchester	Mile End
CO1 1DZ	Feb-09	535	46%	12%	North Hill Surgery, Colchester	Castle
CO7 8PJ	Feb-09	472	17%	14%	The Hollies, Tendring	Great Bentley
CO15 1NJ	Feb-09	367	16%	16%	Ranworth Surgery, Tendring	Pier
CO12 4EX	Feb-09	326	37%	17%	MMC - Wynne, Tendring	Harwich West Central
CO15 3PP	Mar-09	764	29%	9%	East Lynne Medical Centre, Tendring	Pier
CO3 4LN	Mar-09	644	60%	10%	Ambrose Avenue Surgery, Colchester	Prettygate
CO13 9JT	Mar-09	568	32%	12%	CARADOC, Tendring	Frinton
CO1 2DL	Mar-09	370	15%	16%	Wimpole Road Surgery, Colchester	New Town
CO4 4SR	Mar-09	173	47%	24%	Highwoods Surgery, Colchester	Highwoods
CO14 8PA	Jun-09	925	10%	7%	Walton Practice, Tendring	Walton
CO11 2HD	n/a	188	0%	23%	Lawford Surgery, Tendring	Lawford

divided by the total days per month to give admissions per day and seasonal behavior has been adjusted for by applying monthly adjusting factors as described in the methods. The large step-change can be clearly seen, *i.e*. whatever has happened has reached near maximum impact within the space of a month.

The same set of rings were then used to see if age had any effect on the magnitude of the increase and this is presented in Figure 4 where there appears to be a general declining impact between ages 16 to 30 and a general very high impact above age 96. More curiously the effect of age appears to follow a series of peaks and troughs with some ages, most notably, 75, 79, 92 and 69 showing very small increases.

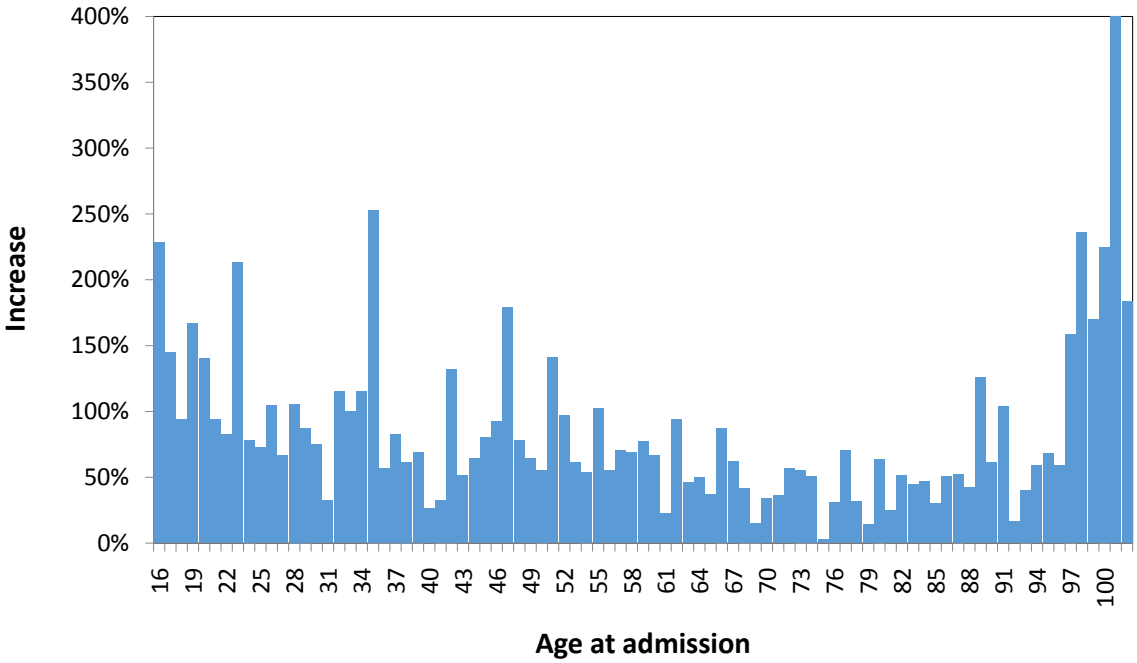
Table 4 then investigates the possibility that particular social groups may be more affected. As can be seen the social group least affected live in an area dominated by student bed sits which experiences no increase in medical admissions, followed by areas of rural light industry and younger affluent families. The areas' most greatly affected contain higher proportions of elderly especially blue collar workers and more deprived residents living in public housing.

Figure 5 investigates if the destination at discharge has any impact on timing or extent. As can be seen those who are characterized by the need for a care/nursing home show initiation as early as June 2008 and have a very high increase in admissions which does however tail off,



*Data covers rings with onset in October, November and December of 2008, i.e. 2, 5-8, 17, 20-22, 26 with monthly admissions divided by days per month.

Figure 3. Monthly admissions (per day) for the rings with initiation in October, November and December.



*Data covers rings with onset in October, November and December of 2008, i.e. 2, 5-8, 17, 20-22, 26.

Figure 4. Effect of single-year-of-age on the magnitude of the step-like increase in admissions.

presumably due to higher numbers of deaths. Those who die in hospital seem to initiate around November but show a lesser increase than those who are discharged back to their home or usual place of residence. Admissions from (and returning to) prisons, psychiatric institutions and facilities for those with learning disabilities all show no change (data not shown), *i.e.* are not affected by the outbreak. These sources of admission represent a segment of the population having least contact with the rest of the general population.

Finally Table 5 investigates if the step-increase is specific to particular body systems. If this is a true infectious outbreak then pockets of diagnoses could be hidden across all specialties. In this table emergency admissions to any specialty and with any length of stay have been analyzed by looking at the ICD-10 chapter of the primary diagnosis for the admission. As can be seen the effects of the outbreak appear to stretch across multiple body systems. Further analysis at ICD 3 digit level of the 100 highest volume diagnoses shows that some 53

Table 4. Characteristics of output areas (OAs) grouped by output area classification (OAC).

OAC	Description	Step-like Increase	97.5% CI	Minimum admissions	Apparent Initiation
2a1	Transient: Student Bed Sits	0%	n/a	113	n/a
3c1	Well-off rural manufacturing	9%	14%	473	Feb-09
2b1	Settled in the city: Gentile flat land	14%	12%	538	Apr-09
6b1	Least divergent	20%	11%	599	Sep-08
4a2	Prospering younger families	20%	19%	280	Oct-08
2b2	Professional town families	20%	23%	190	Jan-09
4c1	Prospering semi-detached	23%	6%	975	Dec-08
6d2	Aspiring redeveloped established areas	23%	13%	511	Dec-08
5b2	Older workers: Public rented and flats	23%	6%	1018	Jun-08
4d2	Thriving suburbs	24%	6%	1990	Nov-08
4b1	Prospering older families	25%	7%	1608	Jan-09
1c1	Older Blue Collar	27%	12%	533	Feb-08
1b1	Younger blue collar	27%	13%	511	Nov-08
6c2	Young families: Deprived bed sit land	28%	14%	431	Feb-09
3a2	Poorer countryside	28%	11%	622	May-09
6a1	Settled households: Hard working	28%	16%	386	Jan-09
3c2	Pleasant rural retirement	29%	8%	862	Nov-08
4b2	Prospering older families	30%	16%	355	Jun-08
6b3	Least divergent	31%	7%	905	Nov-08
3b1	Agricultural: not tied to the land	31%	13%	520	Aug-08
5b4	Older workers	33%	19%	268	May-09
6c1	Young families: Bed sit land	33%	23%	192	Feb-09
3a1	Working villages	34%	12%	562	May-09
4b4	Prospering older families	35%	15%	407	Oct-08
6d1	Aspiring households: well off	39%	18%	301	Mar-08
5a1	Senior communities	40%	26%	146	Feb-09
5b3	Older workers	46%	12%	553	Oct-08
4b3	Prospering older families	47%	24%	168	Feb-09
6b2	Least divergent	48%	7%	876	Nov-08
1c3	Older Blue Collar	51%	17%	348	Jan-09
5b1	Older workers: Public rented and flats	52%	22%	206	Mar-08
5a2	Senior communities	53%	22%	211	Nov-08
4c2	Prospering semi-detached	54%	7%	947	Oct-08
5c3	Public housing	61%	27%	136	Mar-09
4d1	Thriving suburbs	76%	30%	107	Mar-09
1c2	Older Blue Collar: Public rented	81%	30%	106	May-09

diagnoses with 6,661 admissions per annum can be positively excluded compared to 1,602 admissions in 44 diagnoses which are strongly affected (data not shown), *i.e*. there are condition specific effects as well as conditions which remain unaffected. Why this could be possible will be explored in the discussion.

Discussion

In England, Primary Care Organizations (PCO) pay acute hospitals on a cost-per-case basis using the NHS tariff for services called the Health Resource Group (HRG) Tariff. Medical group emergency admissions account for around 18% of the entire inpatient volume (including day case, mental health and maternity) and hence a 24% increase in medical admissions will lead to an approximate 4.4% increase in the total inpatient costs. Such a large and unexpected increase will be financially crippling and this was indeed the case in NE Essex [16,17]. These outbreaks occur across the whole of the UK and it has been estimated that total costs rose by a minimum of £600 million following the 2002 and 2007 outbreaks [4,8,12,18]. In the aftermath

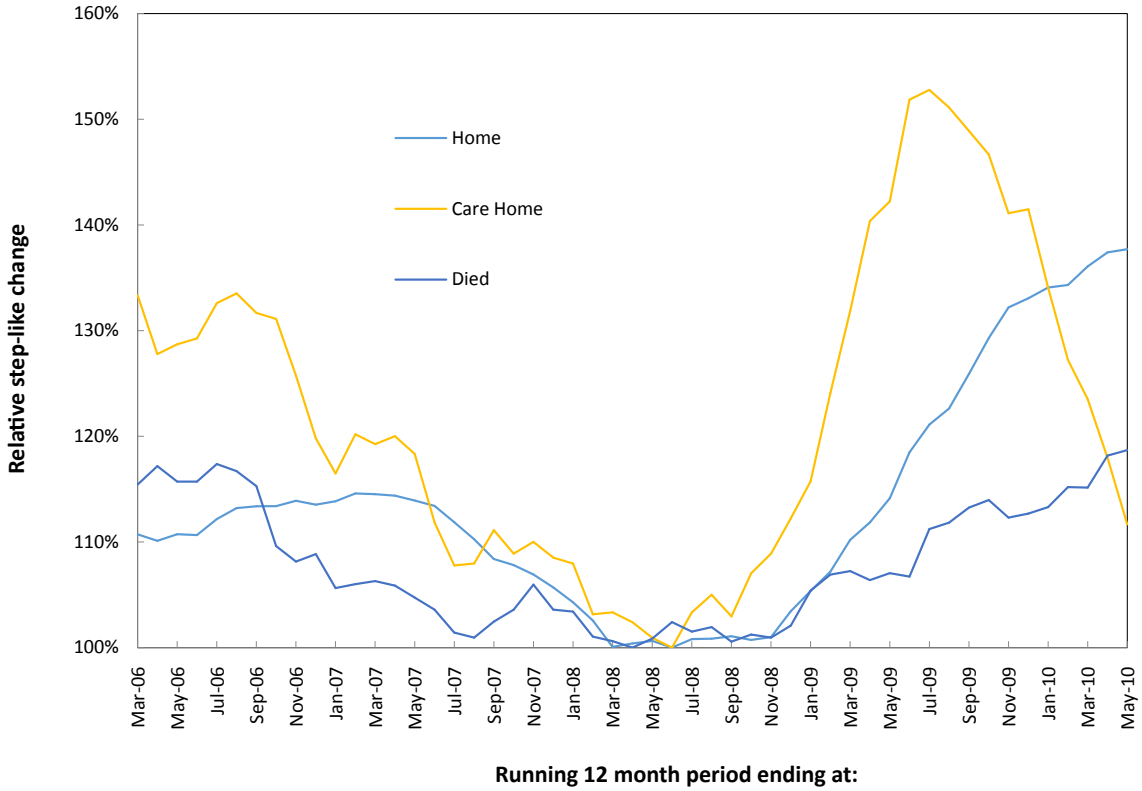


Figure 5. Effect of discharge destination on the time of initiation and extent of the step-like increase as revealed using running 12 month totals.

Table 5.Effect on body systems as summarized by ICD Chapter of the primary diagnosis for the admission.

Chapter	ICD Chapter for primary diagnosis	Step Change (%)	Initiate	Admissions in 209/10 (n)	Step-change (n)
R	Signs & Symptoms	32%	Nov-08	6,156	1,492
J	Lung	22%	Oct-08	3,917	706
I	Vascular	12%	Oct-08	5,946	637
K	Digestive	15%	Nov-08	4,207	549
Z	Health status	16%	Feb-09	3,323	458
S	Injury and Fracture	20%	Jan-09	2,748	458
N	Genito-urinary	14%	Apr-09	2,007	246
G	Nervous System	42%	Sep-08	777	230
M	Musculoskeletal	25%	Nov-08	1,113	223
T	Miscellaneous & external causes	15%	Dec-08	1,418	185
E	Endocrine & metabolic	38%	Mar-09	669	184
P	Perinatal	32%	Feb-09	612	148
A	Bacterial & other	40%	Nov-08	466	133
L	Skin, etc	19%	Dec-08	779	124
D	Blood & blood forming	23%	Jan-09	658	123
F	Mental Health	32%	Mar-09	477	116
B	Viral & other	30%	Feb-09	295	68
H	Eye & Ear	16%	May-09	249	34

*Emergency admissions to any specialty, and including zero day stay admissions.

of the 2007 outbreak the Department of Health (DH) imposed a 70% discount on any emergency activity above the 2008/09 outturn [19], a move which has created huge cost pressures in the acute sector. This cost mitigating measure appears to have been driven by the assumption that 'whatever was happening' was related to acute thresholds to admission [14]. Hence it is vitally important to know exactly what has caused such a huge financial pressure.

The bulk of the analysis presented in this study is for overnight stay emergency admissions, *i.e.* same day or zero day stay admissions have been excluded. There are several reasons for this, namely, zero day stay admissions fall into a grey area between genuine inpatient and emergency department care. This grey area is further complicated by the arbitrary four hour target for treatment in the emergency department in England which, since introduction in 2004, led to a large increase in zero day stay admissions as hospitals opened medical assessment units (MAU) [20,21]. While MAUs are accepted good practice they are also outside of the scope of the four hour target, and hence the validity of such 'admissions' are sometimes questionable [20,21].While this should not be a major issue for admissions to a single hospital the analysis has, never the less, been restricted to those patients with a length of stay encompassing one or more nights and represent those with a genuine need for hospital admission.

While the first method of analysis using concentric rings may be considered arbitrary, the geography of NE Essex is suited to this approach in that the first five rings dissect the town of Colchester, the next rings dissect various farming villages and hamlets and the final rings dissect the three coastal towns. Indeed whatever the method when dealing with a change in admission threshold for a single hospital admissions from any location should show a simultaneous jump which as Figure 1 demonstrates is obviously not the case. That the dates for initiation within the concentric rings are so widely disparate strongly suggests that the hospital itself is not a common focal point for spread of the infection. Indeed the initiation surrounding GP practices in Table 3 is suggestive that these are the most likely focus for infectious spread.

In a running sum, a permanent or semi-permanent step change in admissions due to a reduction in admission thresholds leading to more admissions or due to the introduction of a persistent infectious agent will create a ramp increase which lasts for 12 months. The foot of the ramp marks the point at which the permanent change has been made and the point twelve months on provides the magnitude of the initial step-change. Note that the step-change has to endure for 12 or more months in order to generate the ramp. If the step-change endures for longer than 12 months the ramp is then followed by a plateau as seen in the 3 km and 5 km concentric rings in Figure 2.

When dealing with such a curious phenomenon it is always useful to look back to see if it has occurred before. Indeed such step-like increases which are specific to medical admissions, *i.e.* such trends are not observed in trauma or in surgical specialties, have occurred before in the UK and have been documented around 1993, 1996, 2002, 2007 and again in 2012 [1-10,22]. Even more curiously initiation always appears to commence in Scotland earlier than the rest of the UK [3], and each event not only results in an increase in medical admissions but an increase in deaths, a somewhat non-specific and more variable increase in GP referral and a general increase in health care costs [1-11,22].

The curious step-down prior to the step-increase has also been documented for emergency medical admissions in Northern Ireland [7], for an associated long-term cycle in deaths [3,22], and has been commonly observed by the author in other locations (unpublished). If this is not an acute hospital admission threshold phenomena then what are the alternatives? Firstly, how do we explain the step down which appears to occur elsewhere and also with deaths (all-cause mortality). While 50% of deaths may take place in hospital it is hard to conclude that a tightening of the admission threshold would lead to a reduction in all-cause mortality since the two are largely unrelated. Indeed most hospital deaths are to do with end of life care or, more correctly, the absence of alternative options for end of life care, *i.e.* the person will die with or without hospital care [10,23].

If the cluster of locations with high admissions around November and December of 2008 explain the overall trend observed in Figure 1, *i.e.* the high level trend is driven by a mass effect from the largest locations, then Figure 2 gives a clear indication of how an apparent step-down can likewise occur across a wider geography in that the 22 km ring has commenced a decline some 12 months after the onset of the step-increase. This is also seen in Figure 5 for discharge to a nursing home where there will be high turn-over of residents due to death. Hence the initial step down seen in Figure 1 is a reflection of the tail-end of events following the 2002 outbreak, which similar to the 2007 outbreak may also have occurred later in NE Essex than across other parts of England.

If the step-down arises from the eventual loss of infectious potency, *i.e.* it is eventually bought under immune control, then the step-up must also be explained as part of an infectious spread moving across the whole of the UK along with a step increase in other factors such as GP referrals [24] which have nothing to do with acute admission thresholds. Indeed the highly variable initiation dates ranging from June 2008 through to June 2009 within the concentric rings and other modes of analysis surrounding the acute site cannot be explained by a common acute threshold which would equally apply across all locations at the same time. This is further reinforced by the variable magnitude of the step-change from no change in a minority of small area locations (Table 2) through to very large increases in a minority of other locations.

All analysis presented in the Tables and Figures contradicts the hospital admission threshold hypothesis. My own discussion with hospital Chief Executives and Managers leads to the clear conclusion that the threshold to admission is a clinical decision into which managers do not seek to intrude, other than by the provision of medical assessment units, etc. Research conducted in the USA demonstrates that this clinical threshold is maintained despite considerable fluctuation in the number of arriving admissions and that clinicians manage the resulting bed pressures by flexing the threshold to discharge rather than admission [25].

It is interesting to note that the NE Essex PCT had assumed that the step-down was due to their own efforts and were very proud of the fact that they had the lowest level of age-standardized medical admissions in the East of England. Subsequent analysis revealed that the step-up had merely occurred earlier in other locations in the East of England [16,17], leaving the PCO with the incorrect perception that they had done something special.

In the UK, GP practices enroll patients from a defined area and the only exception is for patients who subsequently move and wish to stay with the practice. In NE Essex GP practices therefore have patients

from 9 to 37 MSOA (23 median) and one MSOA (E02004581) has admissions from 32 practices, however, the largest practices have 20% to 50% of admissions from just one MSOA rising to 90% in some of the smaller practices. Hence interpreting data at practice level reflects the combined effect of varying degrees of distributed populations, and once again the overall trend will be largely driven by the one or two MSOA with the largest number of admissions.

It has been suggested that the infectious agent is most probably cytomegalovirus (CMV). CMV is a ubiquitous herpes virus with a multitude of genes dedicated to immune evasion and subversion [1-2,26] CMV has been implicated in autoimmune disease [26-28] as an oncomodulatory and oncogenic agent [29-32] and is associated with very high mortality rates especially in those with high levels of anti-CMV antibodies and/or with an associated inflammatory response and in the elderly [33-38].

Do the broad effects against almost every body system shown in Table 5 support the CMV hypothesis? There are several key observations which suggest that this could be true.

1. CMV is known to increase all-cause mortality, *i.e.* the cause of death covers all ICD chapters. One study among elderly Latinos demonstrated 43% higher all-cause mortality in those with CMV IgG antibody levels in the upper quartile range while this group also had 35% higher mortality from cardiovascular disease [34]. Another study in Norfolk, England demonstrated 23% higher all-cause mortality in the high IgG antibody group with a 24% increase in death due to cardiovascular disease, a 13% increase in death due to cancer, and a 35% increase for the remaining causes of death, of which 12% had respiratory diseases, 16% gastrointestinal and 21% nervous system disorders [35]. Another study on the elderly in Nottingham, England calculated a sub-hazard ratio 94% higher for cardiovascular death for those with CMV infection and 21% higher for respiratory death [37]. A study comprising a representative sample of US nationalities demonstrated a 30% increase in both all-cause and cardiovascular mortality in CMV seropositive individuals with high C-reactive protein (CRP) levels [33]. Based on the simple fact that nearly 50% of people die in hospital [23], and that the bulk of a persons' lifetime hospital admissions occur in the last six months of life [23], the fact that CMV is so widely implicated in all-cause mortality would suggest that a CMV outbreak would therefore affect admissions for a wide range of diagnoses.

2. CMV is known to have potent effects on immune function affecting both autoimmune functions [26-28], and inflammatory pathways [28,32-37]. There are over 100 known auto-immune diseases and over 100 inflammatory diseases and so the potential to predispose individuals to a wide range of such diseases leading to increased hospital admission in the face of a CMV outbreak is likewise feasible.

3. Systematic reviews of hospital admissions and death where CMV was the confirmed causative agent in non-immunosuppressed patients demonstrated that the gastrointestinal tract and central nervous system were the most frequent sites for severe infection, while other common organ-systems included hematological disorders, thrombosis, ocular and lung disease [28,38]. Once again this list is consistent with Table 5 and the additional analysis of individual diagnoses.

4. A large increase in admissions for Signs and Symptoms, *i.e.* where the diagnosis is somewhat vague, has been noted to commonly accompany these outbreaks [1,5-7], and given the general lack of awareness for the wider role of CMV in hospitalization and death [1,2] many of these admissions are likely to be CMV-related but will lack appropriate diagnostic tests to confirm the real source.

5. CMV is known to infect the thymus with resulting tissue damage and thymopoiesis [1,2]. Recent research has demonstrated that thymopoiesis is associated with a systemic inflammatory state in the elderly [39], and that both thymic output and level of CRP are independent predictors of the time to end of life [40].

In this respect the list of diagnoses identified as possible candidates for a step increase appear to have a CMV link. Links with type I and II diabetes have been implicated in a number of studies [32,41-44], and the increase in admissions for both type of diabetes suggests an agent capable of exacerbating such conditions in a clinical context. Evidence for active CMV infection is common in patients with liver cirrhosis 45 and once again we have an agent capable of at least exacerbating the condition in patients. Epilepsy and Intestinal disorders are characteristic diagnoses identified for these outbreaks [1-2,28], and in the individual diagnoses noted for NE Essex there were additional clusters of cardiovascular (angina, myocardial infarction, ischemic disease, atrial fibrillation and intercerebral hemorrhage), intestinal (diverticular disease, intestinal disorders, alcoholic liver disease, pancreatitis and other digestive disorders), lung (pneumonia unspecified, asthma, pleural effusion), and a nest of signs and symptoms (pain in throat and chest, abdominal pain, nausea, syncope, convulsions) all of which are highly indicative of CMV [28].

Also implied in the results of Table 5 is the concept of a disease progression as a time cascade. That such a time-dependent cascade could exist has been inferred from a study of GP referral to different specialties across the UK following the 2007 outbreak [12], from the peak in outpatient attendance for various dermatological conditions [46], and from the time trends for first diagnosis of particular cancers in the USA [47]. Such a time cascade would arise out of the time-dependent effects upon the immune system mediated inflammatory and auto-immune functions. These preliminary results will hopefully act as the catalyst to further research.

A further interesting issue relates to the apparent saw tooth behavior seen in Figure 4 for the relative increase in medical admissions and age. Such a saw tooth pattern is typical of that seen in what has been called 'original antigenic sin' [48,49]. This arises when the body is exposed to the first of a number of different strains of the same agent. The immune response is 'primed' to the first strain and this priming may help or hinder in subsequent exposure to different strains, hence the series of peaks and troughs which depend on the timing of different outbreaks and the number of outbreaks to which individuals have been exposed.

While the public health implications of this study should be widely apparent there are equally profound implications to funding and the use of age-standardization. These will now be discussed.

Almost all countries use some form of capitation formula to distribute health care funds to various regions and local areas. In the USA such a formula is used to distribute Medicare and Medicaid funds to the various states. All of these formula are based on the assumption that costs are fundamentally driven by population characteristics such as age, gender and deprivation [50]. This work elegantly demonstrates that the medical-related cost of healthcare is modified by the pattern of infectious spread associated with these outbreaks and imply that genuine fair funding requires some form of retrospective adjustment to account for the timing and extent of the outbreak [50,51].

Age-standardization of admission rates relies upon two assumptions, namely, that the most commonly used five year age bands are widely relevant, and the rates within the bands are fairly stable over time. This is called the constant rate fallacy [52]. The very high degree of age-specific behavior which presumably arises from the outcome of 'original antigenic sin' elegantly demonstrates that such age-standardization is highly questionable when applied to the medical admissions so dramatically affected by these outbreaks. This probably explains why age standardization performs so poorly when attempting to forecast future numbers of medical admissions [53], simply because it is the step-like increases which drive the long-term trend, and not the underlying population demography.

The final issue to be addressed is the unique kinetic characteristics of these outbreaks. Fairly slow spread across the entire UK over an 18 month to two year period has been noted for both the 2012, 2007 and previous outbreaks and this corresponds with the relatively difficult to transmit nature of CMV [54] which would imply the introduction of a new strain of CMV [1,2] as per the age-specific behavior suggestive of antigenic original sin. CMV super infection with multiple strains is widely recognized as leading to more averse clinical outcomes [1,2] as implied by this study. How does this reconcile with the apparently rapid spread at local level such that within the space of around one month admissions jump from a lower to higher state? Like all persistent infections CMV is in a state of continuous outbreak and in many instances expresses itself in an acute influenza-like illness [1,2] and associated respiratory illness [55], which in children is statistically more frequent for those infected with CMV [56]. Shedding of the virus is common in both children and the elderly [57-61]. CMV has been detected in the air surrounding patients with CMV pneumonia and to a lesser extent for patients with a 'latent' infection [62], and CMV is known to survive for up to six hours on rubber, cloth and food and has been found on 83/90 wet and 5/40 dry surfaces in day care centers for children [63]. Studies have shown that on average an infected person transmits CMV to two susceptible people [61], and a combination of the above is likely to explain the mini-epidemics of CMV illness described in a neighborhood, renal transplant unit, a laboratory, in burns units and an elderly care ward [64-68]. The particular nature of the infectious spread for nursing homes and GP practices identified in this research strongly suggest that both of these may be acting as loci for the bursts of rapid epidemic-like local spread.

Conclusions

A phenomenon with infectious-like spread has been shown to dominate the time-dependent admission trends for specific medical conditions subsequent to a UK wide infectious outbreak commencing in 2007. This spread has all the characteristics of a genuine infection with a high degree of age specificity, spatial granularity, higher impact on locations with higher density of the elderly, especially the more socially deprived or to nursing home residents. The pattern of conditions most affected points to the involvement of CMV although this requires confirmation. Given the huge financial impact of these outbreaks [4,18,69] research is urgently required to establish whether CMV is the ultimate cause and hence what public health measures can be implemented. Indeed these results add weight to the infectious basis for many diseases [70-72], although genetic and lifestyle factors are also important. There are profound effects upon health care finances, the equitable allocation of funds and the calculation of health insurance premiums. There are additional wider implications to age standardization of admission rates and to standardized hospital mortality rates.

Postscript

This paper was initially peer reviewed and accepted for publication in the 2014 edition of 'Biomedicine International'. This journal ceased publishing in early 2014, and the original publication has now been kindly published by FGNAMB. Since 2014 additional small areas studies have been conducted confirming the results in this study. One of these studies has been published in FGNAMB 1(2): 42-54. These and other papers on these infectious-like outbreaks can be most easily located using a search engine such as Google Scholar.

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