Infectious-like Spread of an Agent Leading to Increased Medical Admissions and Deaths in Wigan (England), during 2011 and 2012

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Author's contribution

The entire work was conducted by the author RPJ.

ABSTRACT

Aims: To demonstrate infectious-like spread of an agent leading to a period of higher death and medical admissions in the Wigan local authority, part of the greater Manchester area of England, during 2011 and 2012.
Study Design: Longitudinal study of deaths and hospital admissions.
Place and Duration of Study: Deaths (all-cause mortality) for the resident population of Wigan from January 2006 to February 2014. Patients admitted to the Wigan Infirmary, a large acute hospital on the outskirts of Manchester, England, between 2008 and 2013.
Methodology: Running twelve month totals for deaths and medical admissions were used to detect step-like increases in these factors. Additional analysis by age, length of stay and for clusters of persons living in over 40 small areas (called mid super output areas) containing approximately 5,000 population within Wigan and surrounds.
Results: A step-like increase in total deaths can be seen for all-cause mortality in Wigan commencing around February of 2012. Medical admissions to the hospital also show a step-like increase at this point. Deaths and medical admissions remain high for around 15 months before beginning to abate. Infectious-like spread of medical admissions can be observed within 40 small area population groups in Wigan during the period January 2011 to April 2012. Certain medical conditions appear to be affected earlier than others, and the pattern of increased admissions show evidence of saw-tooth behavior with age, which is indicative of 'antigenic original sin' and which has also been demonstrated for deaths in England and Wales during 2012.
Conclusion: The spread of a previously unidentified infectious agent is implicated in the

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synchronous increases in death (both in- and out-of-hospital) and in medical admissions (some of which result in death). This is not the first occurrence of an outbreak of this agent and urgent research is required to identify both the agent and clarify its mode of action which appears to be via immune modulation. The ubiquitous herpes virus, cytomegalovirus, which is known to have powerful immune modulating properties, may be involved.

ABBREVIATIONS

CI: Confidence Interval; CMV: Cytomegalovirus, an immune modulating herpes virus; ED: Emergency Department; ICD-10:International Classification of Disease, 10th revision; LA: Local Authority; NHS: National Health Service; MSOA: Mid Super Output Area, a collection of OA's containing around 5,000 population; OA: Output area, smallest area to which Census data is aggregated, with around 500 population; ONS: Office for National Statistics.

1. INTRODUCTION

The Wrightington, Wigan & Leigh NHS Foundation Trust (the 'Trust') is a medium sized acute hospital situated in the town of Wigan on the outskirts of Greater Manchester, England. Over 90% of medical admissions are for residents of the Wigan Local Authority (LA). In common with many other parts of the UK during 2012, it experienced an unexpected and unexplained increase in Emergency Department (ED) attendances, medical emergency admissions and consequent bed pressures which coincided with an unexpected and unexplained increase in deaths across England and Wales lasting for around 18 months [1-2]. This was a repeat of similar unexplained increases in deaths which peaked in 2003 and 2008 [3]. On all three occasions deaths showed distinct spatiotemporal spread across the whole of the UK [4-6] and are highly age, gender and condition specific [7-9]. While the peaks in death are the same magnitude as a *large* influenza epidemic, unusual levels of influenza were absent and no adequate explanation has ever been given.

In 2010, a report by the Nuffield Trust [10] had suggested that such increases may partly be due to a lowering of the acute threshold to admission especially for very short stay admissions. The increase in short stay admissions in England coincided with the introduction of the 4 hour target for ED waiting time in 2001 and involved the convergence of two developments. The first was the introduction of specialist assessment units in pediatrics, surgery and medicine where patients were admitted directly into a focused assessment and treatment environment that was part of emerging good practice. These developments collided with the introduction of the 4 hour target where, in some instances, it became easier to 'admit' patients to assessment units to avoid breaching the target [11-14]. Hence the trend in same day stay 'admissions' identified in the Nuffield Trust report were not deliberate acts of lowering the acute threshold *per se* but rather due to the difficulty of aligning the NHS data definitions and the HRG tariff during a period of rapid change [15-16]. However, while such factors distort the national picture, at a local level they become less significant as soon as a relative stable admission process is in place, and this was the case in the Trust at the time of this analysis.

Other analysis of the trends in emergency admissions has determined that such sudden and unexpected increases have occurred previously, and are specific to the medical specialties. They are marked by a set of diagnoses which appear to be immune sensitive, increase with age, have a degree of gender specificity, occur simultaneously with an increase in deaths, GP referral, ED attendance (along with a sudden change in arriving case-mix) and medical bed demand, and occur across the whole of the UK and in other Western countries [17-38]. More curiously they are also associated with a cycle in the gender ratio at birth [39]. Recent reviews of the available studies have suggested that these events could be due to infectious outbreaks involving the herpes virus, cytomegalovirus (CMV). This virus has a formidable array of powerful immune modifying strategies which have been implicated in autoimmune diseases, cardiovascular disease, certain cancers, hospitalization and death [see reviews 40-42].

With respect to the observed trends, it has been noted that deaths in England and Wales unexpectedly increased around February of 2012 and continued at this higher level to around June 2013 after which they reverted back to the more usual levels [1-3]. This increase did however show high granularity with East Cambridgeshire (East of England) showing a 14% reduction (2012 vs 2011) through to a 21% increase in Bromsgrove (West Midlands) [2]. The position with respect to an increase in all-cause mortality in Wigan and surrounding LA's is given in Table 1 and suggests that Wigan and several (but not all) adjacent LA's were a local 'hot spot', especially for the 80+ age group, i.e. where the infectious-like event had an early rather than later initiation [2-3].

Table 1. Change in deaths between 2011 and 2012 calendar years in Wigan and surrounding Local Authorities

Local authority	Age 65+	Age 80+
Warrington	10%	13%
Chorley	4%	12%
Manchester	4%	10%
Wigan	8%	8%
Salford	7%	7%
Blackburn with Darwen	7%	7%
St Helens	5%	5%
West Lancashire	-2%	4%
Bolton	4%	0%
South Ribble	-2%	-2%

In England, census and other data are aggregated at output area (OA) level. Each OA contains roughly 500 head of population of the same social group and is then aggregated up to progressively larger geographies. Aggregation to what is called a Mid Super Output Area (MSOA), which contains around 5,000 head of population, has sufficient emergency medical admissions to conduct statistically robust analysis of trends over long time periods. In an attempt to resolve the issue as to whether we are dealing with a hospital admission threshold phenomena or a new type of infectious outbreak, this study will investigate the timing and extent of increase in emergency medical admissions within the hospital catchment population at MSOA level over the period 2011 to 2013. This is an extension of previous work analyzing small area infectious-like spread following the 2008 event in the North East Essex area of England [43].

2. MATERIALS AND METHODS

Monthly counts of deaths (all-cause mortality) from January 2006 to February 2014 for the residents of the Wigan Local Authority area were obtained from the Office for National Statistics (ONS). Daily data for emergency admission to the assessment unit and to the medical group of specialties (general and elderly medicine, gastroenterology, hematology, rheumatology, oncology, respiratory medicine, nephrology, endocrinology, rehabilitation), were obtained as part of a review of medical bed requirements at the Trust and are used with permission. Admissions did not contain any patient identifiable information, and contained date of admission, age at admission (whole years), MSOA code, length of stay of the entire inpatient period and the admitting diagnosis as coded using the International Classification of Disease (ICD) 3-digit code. Distance of each MSOA to the hospital site in Wigan was calculated as straight line distance. Data for hospital admissions does not extend beyond March 2013.

All trends were analyzed using running 365 day or 12 month sums. This method is particularly suited to identifying the initiation point for a sudden step-like increase in activity which would arise from an infectious outbreak involving a persistent agent or from a step increase in admissions due to a reduction in admission threshold. The method is also particularly suited to the analysis of data which contains seasonal patterns since the running 12 month sum removes the underlying month-of-the-year patterns allowing comparison to be made between a time-series of 12 month totals. To determine the point of onset and value of any step-like change comparison is made between two successive 12 month periods, i.e. January to December 2102 versus January to December 2013. This process move forward one month at a time until the maximum percentage difference is reached and a visual check is performed that the end of a 12 month long ramp has been identified.

The potential contribution from Poisson variation to the value of any step-change was evaluated using Monte Carlo simulation for the ratio of two Poisson distributions, i.e. the likelihood of a change in a running 12 month total arising from chance. The 97.5% confidence Interval (CI) was calculated with 200,000 trials using Oracle Crystal Ball for an annual total (N) of between 100 and 700 in increments of 100. The resulting 7 values were plotted using Microsoft Excel and follow a power function where $97.5\% \text{ CI} = (1.965 \times N^{-0.0891}) - 1$. This equation was then used to calculate the 97.5% CI associated with the step-increase observed in the various locations. Given the fact that a Poisson distribution becomes less skewed at higher numbers, when N>1,000 then the $97.5\% \text{ CI} = 2.7 \times n^{-0.5}$ [43].

3. RESULTS AND DISCUSSION

While deaths in the UK have been observed to peak in the 2003, 2008 and 2012 calendar years it is recognized that this is part of a far wider spatiotemporal spread in deaths which generally commences earlier in Scotland than England [1-6], although within England there are a range of initiation dates at LA level which overlap with Scotland. For consistency these infectious-like events will be referred to by the calendar year in which deaths reach their peak across the whole of the UK. Up to the present international monitoring of increased death has largely focused on the winter months when seasonal influenza and other winter respiratory infections typically lead to spike increases in death and methods have been developed to detect such spike events [1]. However it has been consistently noted that these outbreaks lead to semi-permanent step-like increase in deaths and medical admissions [1-4,17-25] and a method suited to detecting step-like increases therefore needs to be employed.

In a running 12 month sum, the point of initiation of a step-like increase is seen at the base of a 12 month long ramp. A running 12 month total trend for deaths (all ages) in Wigan is presented in Fig. 1 where the increase in deaths associated with the 2008 and 2012 events can be seen. The full extent of the increase is seen at the point 12 month after the start. If the step-like increase continues for more than 12 months then a plateau will follow as can be observed in Fig. 1. Hence at LA level the 2012 event appears to initiate for the *whole* of Wigan around February 2012 and endures for 15 months while the 2008 event initiates around January 2007 and endures for around 16 months. In Wigan the 2008 event therefore appears to initiate earlier than the UK average (more in line with Scotland), and appears to result in more deaths than the 2012 event (difference between peak and trough around April 2009).

The somewhat intermediate behavior in the running 12 month sum from March 2010 to November 2011 arises from the 2009 'swine flu' epidemic which concluded around August 2010 and from a 'bad' winter period around December 2010 and January 2011. Such spike-like events create a plateau (rather than a ramp) in a running 12 month total. There are alternative methods which are more suited to analyzing such spike-like events/outbreaks [1-2]. However, note that there is no 12 month long ramp to indicate a step-like feature; that these intermediate effects have cleared away before the onset of the 2008 event, and that the 2009 influenza epidemic failed to increase deaths to the level seen in the 2008 and 2012 events, i.e. we are dealing with recurring events of high public health significance. Similar intermediate behavior is seen in some of the following figures, and Fig. 1 therefore provides a useful context. In this respect Fig. 2 shows the running 12 month trend in admissions and deaths experienced at the local hospital during this time.

Both admissions and in-hospital deaths commence the step-like increase around February 2012, although the shape of the running sum chart is different to that for all-cause mortality Fig. 1 since in-hospital deaths only account for roughly 50% of all deaths in the UK and will tend to be associated with acute medical conditions/diagnoses. The main point from Fig. 2 is that medical admissions rise almost in parallel to admissions leading to in-hospital death, i.e. the hospital standardized mortality rate is largely unaffected except perhaps very early in the outbreak (February to April 2012) and later (December 2012 to March 2013) when deaths rise faster than admissions. Reasons for this disparity will be discussed later but appear to be related to a time cascade in diagnosis/conditions emanating out of the outbreak.

Having established that the increase in deaths and medical admissions are linked, it is useful to study the trends in admissions in the 40 MSOA which comprise the Wigan LA area. In the past it has been assumed that these step increases are due to hospital-based reductions in the threshold to admission, a proposal which cannot explain the simultaneous increase in deaths, nor the apparent related cycle in the gender ratio at birth. However if this were the case, then admissions would simultaneously rise in all small areas surrounding the hospital. A preliminary comparison of admissions in 2012/13 versus 2011/12 indicated that there was no evidence for a simultaneous jump in admissions, nor any relationship between distance from the hospital, i.e. residents living close to the hospital using the ED as an alternative to primary care, and that there were no length of stay specific issues, i.e. the increase was not due to a change in the use of the assessment unit.
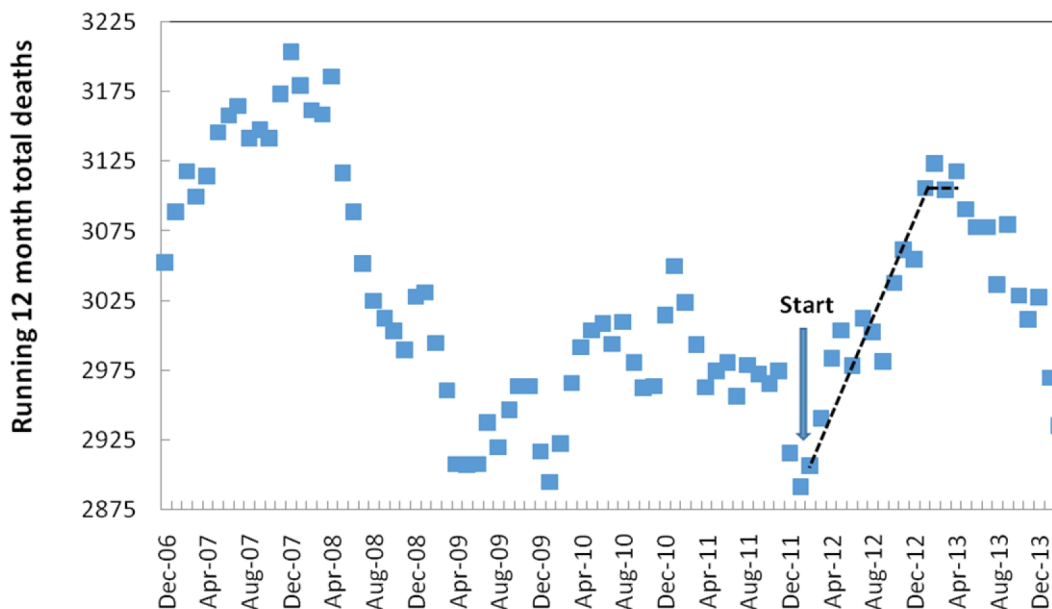
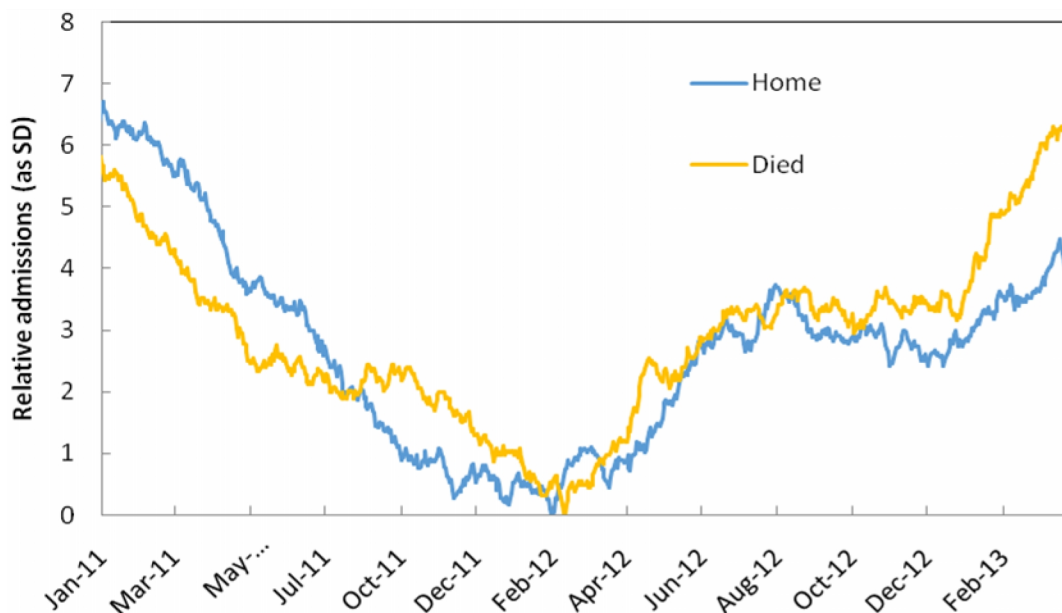**Fig. 1. Running 12 month sum of deaths (all-cause mortality) for residents of Wigan**

Fig. 2. Trend in the running 365 day total of admissions by destination at discharge
Admissions are a running 365 day total and are relative to the minimum over the period. The difference to the minimum point has been calculated as standard deviation's equivalent assuming Poisson statistics where, by definition, one standard deviation equals the square root of the average. On this occasion the average is taken to be the running 365 day minimum number of admissions or deaths which occurs around January 2012

The change in admissions ranged from -14% for MSOA Wigan 016 (5.1km from the hospital) through to +16% in Wigan 002 (3.4km from the hospital). The trend in each MSOA was then evaluated to determine the onset of a step-like increase in admissions and the percentage increase in admissions. Due to the way in which the step-like increase is determined an initiation date of, say Jan-12, implies that the step increase occurs toward the end of the month or even very early in the next month. These results are presented in Table 2 where it can be seen that there are a range of initiation dates commencing in January 2011 through to June 2012.This wide range in initiation dates is highly reminiscent of an infectious spread and it would be very difficult to explain why there should be a series of step-like increases other than from an infectious event. The apparent initiation date around (late) January 2012 for the whole of Wigan is driven by the cluster of 10 MSOA initiating at that time and a balancing effect between other MSOA initiating before and after this pivot point. Indeed the very fact that the hospital and the LA experienced a sudden (and otherwise unexplained) 14% increase in medical admissions is an unprecedented event, especially when this increase then persists for 15 to 18 months.

Poisson statistics describes the random variation around the average for whole number events such as deaths or admissions. The 97.5% confidence interval (CI) shown in Table 1 has been calculated assuming Poisson randomness, i.e. to what extent could a calculated percentage change be influenced by chance. The 97.5% CI has been used to give a slightly higher level of confidence over the usual 95% CI used in many studies. As is expected, those MSOA with higher number of admissions have a much tighter CI and chance can be excluded as a major contributing factor.

Fig. 3 presents running total trends for a sample of MSOA. Points to note are the variable trends downward from the previous winter which will presumably be due to a range of winter respiratory viruses and knock-on bacterial infections. All MSOA exhibit the highly granular effects that would be expected of any infectious event. The size of this previous winter event in each MSOA does not appear to be linked to the size of the 2008 event, i.e. these events are independent. However from a separate study of deaths in English LA's, there is some evidence to suggest that the size of the 2008 and 2012 events may be linked in that LA's experiencing a large increase during the 2008 event show a lesser increase for the 2012 event and vice versa [6]. This is suggestive of some form of linkage perhaps via the death of sensitive individuals.

Up to the present, demographic change (population ageing), has been assumed to be the main driver of hospital admissions. However based on a twenty year career in health care forecasting, the link with demography regarding the medical group of specialties is exceedingly tenuous and other factors appear to play a far greater role. As has been demonstrated the above patterns cannot be explained by hospital threshold to admission, since the behavior depends on location within the hospital catchment rather than the hospital *per se*. Weather and other environmental phenomena can likewise be discounted since all MSOA in Wigan will experience roughly the same weather. Likewise changes in the composition of the population simply do not happen in the sudden step-wise manner demonstrated in this study. The fact that the trend lines for patients discharged home or died in Fig. 2 are roughly parallel is another indicator that whatever is happening is not due to a change in the threshold to admission. If the threshold to admission had reduced then less acutely ill patients would be admitted and the line for discharged home in Fig. 2 would rise more rapidly than that for deaths.

Table 2. Initiation date and percent increase in admissions (with confidence interval) to a variety of MSOA

Location	Initiation	Increase	97.5% CI	Admissions in 2012/13
Wigan 012	Jan-11	14%	11%	587
Wigan 004	Feb-11	17%	16%	355
St Helens	Feb-11	49%	19%	289
Wigan 028/029	Feb-11	16%	28%	120
Other nearby LA	May-11	23%	20%	244
Wigan 019	Jul-11	27%	15%	396
Wigan 026	Jul-11	41%	15%	398
Wigan 030	Jul-11	33%	18%	292
Wigan 023	Aug-11	27%	28%	119
Not Known	Sep-11	20%	9%	718
Wigan 024	Sep-11	30%	13%	502
Wigan 036	Sep-11	10%	13%	517
Wigan 021	Sep-11	17%	15%	424
Wigan 033	Oct-11	35%	12%	539
Wigan 032	Oct-11	24%	14%	471
Wigan 039	Oct-11	21%	17%	331
Wigan 007	Nov-11	60%	17%	351
Wigan 040	Nov-11	66%	16%	366
Wigan 003	Dec-11	42%	13%	485
Wigan 006	Dec-11	48%	13%	476
Wigan 011	Dec-11	37%	13%	486
Wigan 005	Dec-11	14%	14%	462
Wigan 020	Dec-11	20%	14%	434
Wigan 037	Dec-11	39%	18%	313
West Lancashire	Jan-12	32%	10%	698
All Locations	Jan-12	14%	1%	18,928
Wigan 015	Jan-12	11%	8%	811
Wigan 010	Jan-12	27%	9%	739
Wigan 009	Jan-12	19%	8%	795
Wigan 014	Jan-12	37%	11%	612
Wigan 031	Jan-12	57%	12%	577
Wigan 008	Jan-12	15%	14%	450
Wigan 002	Jan-12	40%	13%	482
Wigan 038	Jan-12	13%	14%	443
Wigan 001	Jan-12	39%	20%	260
Wigan 013	Feb-12	15%	12%	561
Wigan 027	Mar-12	21%	13%	481

Table 2 Continued….

Wigan 017	Apr-12	42%	26%	148
Other England	Jun-12	11%	25%	162
Wigan 034	No Increase	n/a	17%	341
Wigan 035	No increase	n/a	15%	425
Wigan 018	No increase	n/a	12%	552
Wigan 016	No Increase	n/a	13%	519

Admissions in 2012/13 are given as an indication of the relative size of each MSOA. Smaller MSOA will have a larger confidence interval and vice versa. The confidence interval is calculated based on the number of admissions in the 12 months prior to the step-like change. The 'Other nearby LA' group excludes St Helens. Wigan 028 and 029, which are adjacent, were aggregated due to small numbers of admissions. The four MSOA at the bottom of the table labelled 'no increase' had not shown any apparent increase within the study period. Initiation at a later date is possible
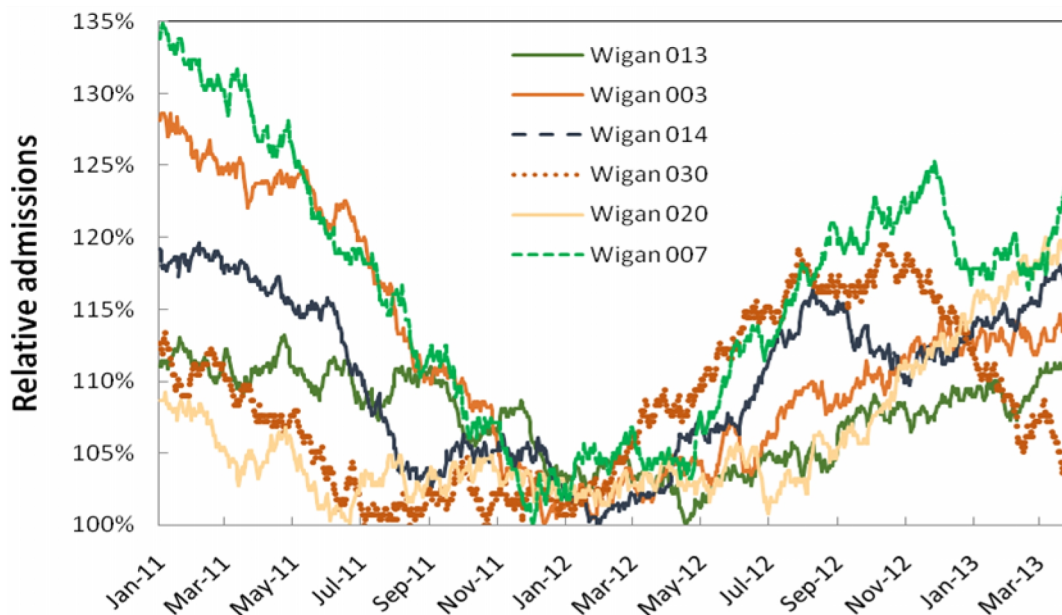

Fig. 3. Running 365 day total trends for medical admissions from a variety of MSOA
Note that infectious events prior to this outbreak have ceased to affect the running 12 month total before the start of 2102, and on this occasion allows a clear view of the outbreak, the onset of which occurs at the foot of the ramp seen in each MSOA. The somewhat jagged nature of the trends is due in part of Poisson randomness and the presence or absence of other events influencing admissions. However on this occasion the contribution from other events are of far less consequence than the particular outbreak of interest

While the apparent increase in deaths occurred around February 2012 in England and Wales, this is known to be part of a wider spread with the increase in deaths commencing first in Scotland as early as August 2011 in the Fife Area Health Board (a large geographic area) [5] and this appears to concur with the earliest onset in Wigan at around January/February 2011 in a minority of MSOA as shown in Table 2. The apparent increase for the whole hospital catchment area does not occur until January 2012, and a similar dispersion in timing will also be occurring in the larger Fife location in Scotland. Such spread

is consistent with the transmission of epidemics via the movement of travelers (air, rail, motorway) followed by the movement of individuals within social networks at local small area level [44-45]. Note that emergency medical admissions (at least for some diagnoses) are a leading indicator of these outbreaks while deaths can lag up to a month behind [5]. Earliest introduction for Scotland and hence parts of the wider UK is probably somewhere around the start of 2011. Note also the generally later date for admissions from the rest of England, "Other England" in Table 2, who will be people on business, holidays or visiting family which are mainly from more southern locations and is indicative of a degree of north to south spread but with isolated pockets of earlier initiation [6].

It is the particular nature of the spatial spread of this infectious agent which gives a clue as to why it has remained undetected for so long. National trends in mortality are usually conducted at LA level for the simple reason that the number of deaths becomes too small for meaningful analysis at sub-LA geographies. A comparison of Fig. 1 (LA-level) and Table 2 and Fig. 3 (both at sub-LA level) reveals how the impact upon death is greatly under-estimated at LA-level. What is seen at LA-level is a composite picture of complex small area spread within each LA. Early initiation in a number of small areas, i.e. the MSOA in the top half of Table 2 pull the base line for the whole LA upward, and the running total for the LA only shows a 7.5% apparent increase in deaths which is far lower than the 8% to 66% (range) increase in admissions seen at MSOA level. Admittedly the link between increased deaths and medical admissions may not be a direct relationship, however the very high granularity at small area, both in terms of initiation date and percentage change, shows how the full extent of each outbreak has been concealed. The extent of concealment will be even greater when using data aggregated at national level [6].

Something similar to an influenza or SARS outbreak can be discounted, since such outbreaks usually last between 8 to 12 weeks and therefore in a running 12 month total chart do not create the 12 month long ramp indicative of the semi-permanent step-increase as demonstrated in this study. The fact that the step-increase endures for 12 months or more is illustrated by the line for Wigan 003 in Fig. 3 where the increase is subsequently maintained from November 2012 through to March 2013, i.e. it has endured at least 17 months. This rise followed by an eventual decline with timing differences between local areas is, what is known in disease epidemic terms, as a travelling wave with spatial hierarchies [46-47].

Analysis of the change in admissions for patients with different length of stay in hospital is suggestive of different phases of an infectious outbreak. First to die are those who are already extremely frail, deteriorate rapidly and die within 24 hours of admission to hospital (data not shown). One month later deaths rise in those with 6-14 day stays and are probably frail but not excessively so, develop exacerbation of existing conditions and die after a moderate period of acute care. That deaths after a 2-5 day stay increase in December is probably a reflection of a subset of the population who experience weakening after 8 to 9 months of exposure and acute illness with death is then triggered by the following winter. This concept was incorporated into the modelling work of Dushoff [48] where the acquisition of the first infection leads to immune weakening with higher likelihood of acquiring a second opportunistic infection after a particular time lag. Whatever the explanation, we are not dealing with a phenomenon that can be explained in simplistic terms of admission thresholds.

A further key observation is the fact that emergency medical admissions are trending downward in the period prior to the proposed infectious outbreak which is contrary to the generally perceived role of the ageing population as the principle driver of ever increasing medical admissions. Such an upward and downward cycle has been demonstrated to be a

part of these outbreaks, and indeed is a fundamental part of a cycle of surplus and deficit seen within the NHS in the UK and in the private health insurance industry in the USA over many years [26,31, see review 49].

Having established infectious-like spread at small area level within the larger LA, it is of interest to see if age and diagnosis play a role in these events. Analysis of deaths in England & Wales associated with the 2012 event, has already demonstrated single-year-of-age saw-tooth patterns reminiscent of what is called 'antigenic original sin', i.e. the consequences of the immune priming effects of repeat exposure to a series of different strains of the same agent [3]. In this respect Fig. 4 presents an analysis of the effect of age upon the difference in admissions for twelve month periods before and after the event.
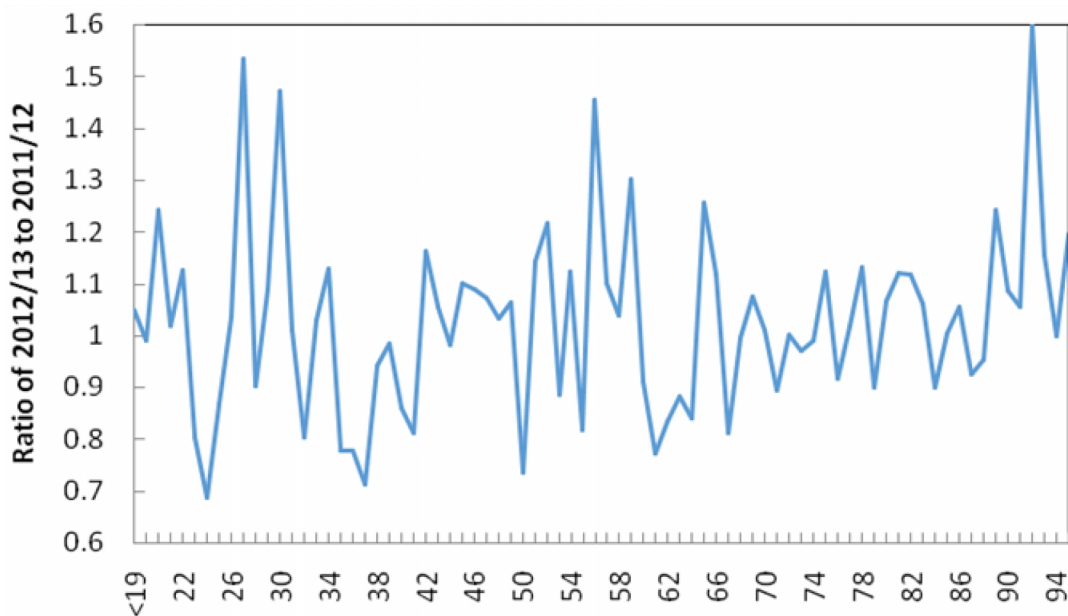

Fig. 4. Ratio of medical admissions in 2012/13 versus 2011/12 by single-year-of-age
Comparison of two twelve month periods is necessary to achieve statistically significant total admissions for each single year of age

As can be seen, the characteristic saw-tooth patterns are evident for medical admissions in Wigan as have been observed for deaths in England & Wales during the 2012 event [3] and for medical admissions in North East Essex during the 2008 event [43]. The implication is that the infectious events are due to different strains of the same agent, and that an immune response is involved. A further clue to immune involvement is given in Table 3 where a time cascade in diagnoses appears to be associated with the infectious-like event.

The possibility of a disease cascade following these outbreaks has already been suggested from a study of increased GP referrals associated with the 2008 outbreak and of outpatient attendance for specific dermatological conditions [32,34,36-37]. Another study also suggests that the 2012 event led to a shift in outpatient case-mix toward immune sensitive conditions [50] while admissions for the more aggressive forms of tuberculosis appear to lag some three years behind these outbreaks [51]. Based on a match with the diagnoses which increase during these outbreaks and are associated with increased death, the herpes virus

cytomegalovirus (CMV) has been suggested as a possible causative agent [4,7-9,40-42]. This virus possesses a formidable array of immune evasive and modulating strategies which are implicated in hospitalization and death [40-42,52-53]. In the USA a set of CMV-sensitive cancers appear to show a cycle of incidence induced by these outbreaks [54].

Table 3. Initiation date and percent increase in admissions for diagnoses associated with the infectious-like event

ICD	Description	Initiation	Increase
K92	Other diseases of digestive system	Jan-11	39%
B34	Viral infection of unspecified site	Jan-11	115%
I21	Acute myocardial infarction	Jul-11	68%
K80	Cholelithiasis	Sep-11	22%
O23	Genitourinary infections in pregnancy	Sep-11	50%
K59	Other functional intestinal disorders	Nov-11	42%
T81	Complications of procedures NEC	Feb-12	24%
J18	Pneumonia organism unspecified	Mar-12	41%
L03	Cellulitis	Mar-12	23%
O26	Pregnancy related conditions	Apr-12	12%
J45	Asthma	Apr-12	14%
R06	Abnormalities of breathing	Apr-12	16%
S01	Open wound of head	Apr-12	14%
O68	Labor complicated by fetal stress	May-12	19%
R10	Abdominal and pelvic pain	Jun-12	30%

Analysis at the level of a single diagnosis is generally hampered by small numbers. Further studies on the possibility of disease cascades will need to cluster MSOA with the same initiation point to amplify the exact nature of the cascade

With respect to the issue of CMV, Table 3 is illuminating, since it encompasses a range of conditions known to be CMV sensitive [40-42,53]. The disease cascade is initiated with admissions for an unknown virus and/or non-specific gastrointestinal problems around January of 2011 and CMV-mediated vomiting, diarrhea, enteritis, colitis and inflammatory bowel disease is well recognized [53,55-57] as is the role of CMV in cardiovascular disease [58-59] and fatal myocarditis [60]. The cluster of respiratory conditions around March/April 2012 is also consistent with the lung as a major source of CMV infection [9,61] as is the role of CMV in allergic asthma [62]. The issues relating to pregnancy are likewise expected given a cycle in the gender ratio at birth which appears to accompany these outbreaks [39] and the well-recognized role of CMV in infection and complications during pregnancy [63-64]. The female genito-urinary tract is a well-known locus for CMV infection [64-65]. Such a progression of different diseases could be indicative of sites of direct infection and/or hastening of particular conditions via immune mediated effects against inflammation and autoimmunity [40-42]. An increase in admissions for 'open wound of head' (ICD S01) is indicative of a by-stander condition. This diagnosis is part of a wider cluster of upper torso injuries and fractures (unpublished), suggestive of increased falls among the elderly due either to the clumsiness associated with a generally higher level of illness during an infectious outbreak, or to giddiness which would link to the neurological aspects of CMV infection [8,40-42,53]. The apparent time cascade in conditions presented here is similar to those seen in North East Essex after the previous 2008 outbreak [43]. While the direct link with CMV awaits confirming studies, it would appear that a disease cascade could be a characteristic feature of these outbreaks.

More detailed analysis of cause of death has not been conducted in this study simply because the numbers are too small for statistically meaningful conclusions. However, several recent studies have been conducted on the increase in deaths during 2012 for the whole of England and Wales. Notable increases in death for those suffering from neurodegenerative diseases (mainly dementia, Alzheimer's and Parkinson's) and for respiratory conditions [8-9] have been characterized. A paper investigating increased digestive system deaths is currently in preparation. In all cases the conditions/diagnoses associated with increased death appear to be sensitive to CMV-mediated exacerbation.

This study raises important questions regarding the hidden assumptions behind age standardization of admission rates and hospital mortality rates. Almost all age standardization used in health care employs five year age bands, and it is assumed that there is no hidden spatiotemporal spread of an agent capable of influencing medical admissions and deaths to the extent demonstrated here. The author has noted that particular hospitals in England were temporarily flagged as showing 'high' death rates for pneumonia during the 2012 event. It has been suggested that the unique spatiotemporal pattern of spread for this outbreak arises from some form of respiratory phase which enables the very rapid local spread seen in the step-like increases [9,43]. Since pneumonia is one of the most common causes of in-hospital death, the highly granular nature of the spread across the UK combined with the single-year-of-age saw-tooth nature of the increase will invalidate the assumptions lying behind age standardization of hospital mortality and the seemingly sporadic flagging of hospitals will result, especially for pneumonia. Indeed it was such sporadic flagging of apparent excess mortality at this hospital, which has an otherwise exemplary record, along with the accompanying increase in medical bed occupancy which gave the impetus for this study. Given the link between marginal changes in death and medical admissions seen in Fig. 2 and demonstrated elsewhere [33,66], this work also raises questions regarding the hidden assumptions contained in the NHS (England) funding formula [67].

As with any study there are several limitations worthy of comment. The use of a running 12 month sum is adequate for the detection of a step-like change in admissions and deaths, however, future studies will need to employ a range of alternative methods to further characterize the spread of this agent and strip out any simultaneous contribution from temperature changes and/or other infectious outbreaks which may overlap with the 12 to 18 month period in which admissions and deaths remain high. At the present CMV is not a notifiable infection and detailed studies will be required to determine, if and how, this agent is involved. If a new strain is implicated then both genetic and viral surface glycoprotein changes could be implicated, and this will necessitate appropriate methods over and above the usual measurement of anti-CMV IgG and IgM levels in blood.

It is probably apposite to ask why it has taken so long to recognize the existence of these infectious-like outbreaks. Unusual events such as these are not new. In 1969 the Western Infirmary in Glasgow reported a 27% increase in medical admissions in the six months August 1969 to January 1970 compared to the same period a year earlier [68]. A similar large increase also seems to have occurred in Scotland in late 1984 or early 1985 [69]. In the financial year 1993/94 emergency admissions across England had increased by 7 to 13% compared to 1992/93 [70-71]. At the Aintree hospital in Liverpool there was a 37% increase in medical admissions with an unexpected large increase in the 15 to 44 age group, while in nearby Manchester admissions to one mental health hospital increased by >30% [70]. Parallel increases in medical and mental health admissions were replicated across the whole of England, and medical admissions at the Royal Berkshire Hospital increased

unexpectedly by 13% commencing in the middle of March 1993 [72] as did the number of occupied medical beds [73]. Events such as these are usually dismissed as having little relevance to present day changes and pressures in the NHS. Unfortunately in the absence of the knowledge of infectious-like spread, a host of studies into these events assumed that the 'problem' was due to a mix of social change and the inability of health service organizations to manage demand [74-77]. While such factors are important in the correct context, they do not lead to large step-like increases in emergency admission, however, such thinking had become so entrenched, that all rises in emergency admission are interpreted from that framework.

Hence the report by the Nuffield Trust suggested that increases in emergency admissions between 2004/05 and 2008/09 were largely due to a reduction in admission thresholds [10]. However, this (unproved) assumption contradicted the conclusions from two earlier studies. In the first, research in the USA had demonstrated that acute admission thresholds are maintained despite considerable fluctuation in demand [78], while in the second it was suggested that emergency medical admissions only ever rose in sudden spurts [19-20], as per the reports cited above [68-71]. Indeed the data presented in the Nuffield Trust report shows evidence for one such spurt of growth at the end of the study period although the significance of this seemed to have been overlooked, but was noted by others [79]. Given the evidence presented in this study, it would seem that preconceived notions may need to be re-evaluated.

These are initial studies conducted in an attempt to explain an otherwise poorly understood phenomena. The results need to be confirmed over wider geographies, and a continuous study over the period 2000 to present would be useful to identify both the 2003, 2008 and 2012 events. Given that it is far easier to demonstrate statistical significance in MSOA with >300 admissions per annum, the aggregation of MSOA with a common initiation date will assist in such studies although this criteria is more readily met in more densely populated urban areas. Such aggregation will further facilitate analysis of cause of death and possible time cascades in both admission and death. It has also been suggested that an outbreak of this agent earlier in the year acts to potentiate the effect of seasonal influenza during the following winter [17-18,43]. This preliminary study will hopefully stimulate further research.

4. CONCLUSION

Evidence has been presented to show unique spatial behavior within Wigan leading to increased emergency admissions at the time that deaths were observed to increase at a local and national level. Acute admission threshold changes can be categorically ruled out as the cause. The cause of the increase shows small area spread, and the characteristic saw-tooth pattern of change in admissions with age is suggestive of antigenic original sin. At the very least, emergency admissions are defying all known models relating to supposed demographic change. The unusual trends seen at larger geographies such as primary care organizations, acute hospitals, regions, state and whole country, are the composite of the small area spatiotemporal trends. Infectious spread of an unrecognized agent is a likely cause and requires further urgent investigation. The ubiquitous herpes virus, cytomegalovirus, could be involved but this requires further study.

CONSENT AND ETHICAL APPROVAL

Patient consent was not required. Ethical approval was not required. No patient identifiable data was used in this study.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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