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Recurring Outbreaks of an Infection Apparently Targeting Immune Function, and Consequent Unprecedented Growth in Medical Admission and Costs in the United Kingdom: A Review

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Author's contribution

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

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Review Article

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ABSTRACT

Background: The National Health Service (NHS) in the UK has been beset by unprecedented growth in emergency admissions to hospital which are specifically medical in nature, while surgical and trauma admissions are only showing the level of low growth expected from demographic change, or what is called the ageing population. There has never been an adequate explanation for this dichotomy.
An Infectious Basis: The proposed infectious basis rests upon the observation that growth in medical admissions occurs in spurts which occur approximately five years apart, albeit three years between spurts have also been observed during the 1990's. It is these spurts which are driving the long-term growth, rather than the relatively minor growth which occurs in the interval between the spurts. These periods of high growth are characterized by spikes in all-cause mortality, and typically result in a 15% increases in admissions to the medical group of specialties. However much higher growth is seen for particular conditions/diagnoses which appear to have a common

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immune function basis via infection, inflammation and autoimmunity. These outbreaks can be seen across Europe, and the last three outbreaks commenced around Mar-02, Mar-05 and Mar-10 with subsequent spread over the next two years. The middle of these three outbreaks had the lowest increase in deaths and medical admissions.

Implications: There is now an overwhelming body of evidence pointing to a recurring series of infectious-like events. In the UK, the 2012/2013 outbreak led to 45,000 extra deaths while across the 27 EU countries, each outbreak appears to result in somewhere in excess of 467,000 deaths. In Europe, the outbreaks tend to occur earlier in Denmark, Romania, Bulgaria and Slovakia, while they tend to occur later in the UK, Belgium, Greece and Slovenia. Emphasis now needs to switch toward clinical studies which screen the population for changes in the levels of specific IgM and IgG antibodies against a range of potential candidate organisms, and post mortem examination of the tissues of persons who die from a particular range of conditions such as neurological disorders including dementia and Alzheimer's; respiratory and gastrointestinal tract diseases, and cardio/vascular conditions.

Conclusion: This new disease has the potential to be a highly disruptive discovery involving changes in fundamental health care policy, and our understanding of the role of immune function in the exacerbation of a range of common medical conditions.

Keywords: Increasing medical admission; death; emerging infectious diseases; immune impairment; cytomegalovirus, gender; age; health insurance underwriting cycle; health care costs; health care policy.

1. INTRODUCTION

In the area of mathematical modelling, it is widely recognized that all models contain hidden assumptions, and that it is therefore vital to recognize and understand the impact of such assumptions on the performance of the model. Indeed how we view the world, relies on our hidden assumptions regarding how things work, and this is especially so in the area of health care. Government policy is, for example, crafted around such assumptions. In England, the current Conservative led coalition government sees privatization and free market efficiency as a route to cost saving. However what happens if these assumptions are even partly incorrect?

Rising medical admissions have been observed since the 1980's and even earlier. There was a 45% increase in Scotland between 1981 and 1994 [1], an 85% increase in Bournemouth between 1992 and 2001 (25% between 1997 and 2001) [2], an 80% increase in admissions via the emergency department in Sheffield between 1988 and 1995 [3], and a 45% (Hull), 65% (Scarborough) and 75% (Sheffield) increase respectively in admissions via the emergency departments between 1987 and 1997 in the north of England, where the proportion admitted rose from around 9% to 17% in the same period [4], and an 86% rise in age 75+ admissions between 1990 and 2000 in Gloucester during a time when the age 75+ population only grew by 24% [5]. Fig. 1 gives a more recent picture of the continuing increase over the 14 year period ending 2012/13, where the increase seen in the surgical group is reasonably close to that expected from demographic change. Recall that surgical interventions may be required to correct the result of medical conditions, i.e. atherosclerosis, etc.

Up to the present, the rapid growth in acute demand has been explained by factors such as supply-induced demand, an ageing population, the elderly living alone, conservative GP and hospital consultant behavior, health care consumerism, rapid advances in technology and increasing complexity of treatable conditions, the failure of health care organizations to 'manage' demand, lack of integration between health and social care and ease of access to primary care [5-18]. Whilst not denying that such factors have a role, generally speaking, to require acute care a person has to be genuinely ill or via an outpatient consultation have a condition requiring specialist diagnosis.

During a 22 year career investigating health care trends for the purpose of capacity and financial planning, it became evident that rather than growing steadily, growth in emergency medical admissions occurs in spurts. Specifically that the spurts were restricted to medical conditions rather than surgical or trauma conditions, where growth seems to follow a more stable and continuous trend, as would be expected from changes in population demography [6-7,19-20].

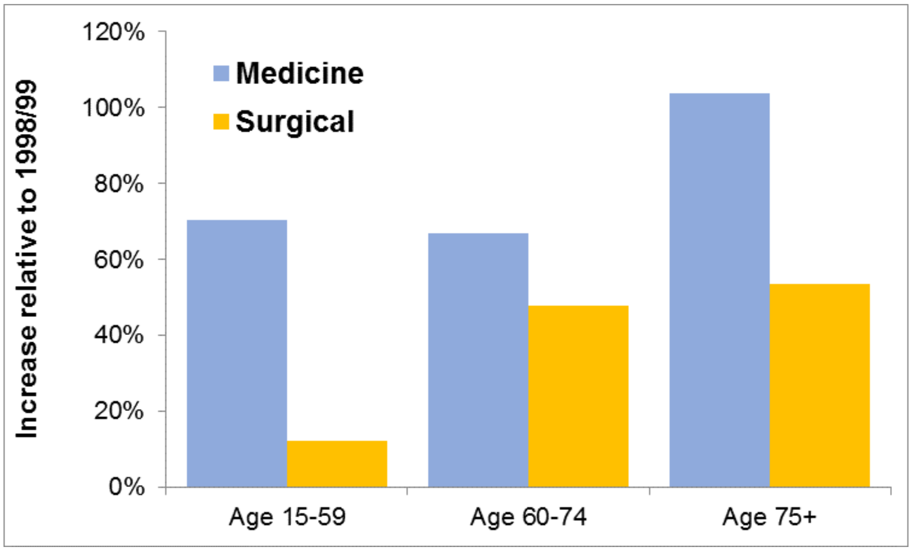

Fig. 1. Increase in medical and surgical group admissions between 1998/99 and 2012/13 in England

Data is from Hospital Episode Statistics http://www.hscic.gov.uk/hes and covers both elective and emergency admissions. Surgical group includes general and other surgery, ophthalmology, ENT, oral and maxillofacial surgery and trauma and orthopedics. Medical group includes all medical specialties (excluding pain management and accident and emergency which were subject to counting changes)

Obviously there have been exceptions, and policies to encourage fewer people to smoke, for example, have had positive effects. Likewise the use of statins, drugs to control blood pressure and stomach ulcers, primary care management of diabetes, and the move to manage mental health conditions in the community. Hence, in England some 46 primary diagnoses (ICD-10 three digit level) with over 1,000 admissions per annum across England, have shown greater than a 40% reduction in total admissions over the 14 year period 1998/99 to 2012/13 (7% dropping to a 3% share of total admissions). However, over the same period some 210 primary diagnoses have shown greater than a 100% increase in admissions (15% increasing to 30% of total admissions).

It is virtually certain that in England, some of the increase will have been driven by the unintended consequences of policy. Hence under Payment by Results (PbR), a fee for service tariff similar to the DRG tariff in the USA, there was a large expansion in non-surgical 'day case' activity which exploited a flaw in the tariff that paid this kind of elective activity at the average cost of all lengths of stay [21-22]. The introduction of an arbitrary four hour target for a stay in the emergency department, also led to a large increase in same day stay emergency 'admissions' [23] – a shift which was also driven by flaws in the tariff [24-28]. However even after adjusting for these effects there are still around 100 primary diagnoses, of a medical nature, which are showing unprecedented growth, especially among the elderly, and with marked cyclic 'spurt' growth behavior [29-30].

Following the 2007 'spurt' which reached a peak in England in the 2008 calendar year, the Department of Health (England) introduced a 70% discount to the tariff for emergency admissions which commenced at the start of the 2010/11 financial year and was based on the volume of emergency admissions above that for 2008/09 activity, i.e. the year that the outbreak peaked [31]. The NHS (England) operating framework for 2010/11 stated that the rule was, "in support of the shift of care out of hospital settings, and to encourage closer working between providers and commissioners" [32]. Although not stated, the hidden assumption was that acute hospitals had somehow reduced their threshold to admission and that financial penalties would force them to 'reform'. Did no one at the Department of Health (DH) consider the possibility that the huge rise in medical admissions and costs may have had fundamental significance? Rather than being merely an issue of health service 'inefficiency' did no one consider the possibility that the patients may have been genuinely sick, and that the real reason may have been an unrecognized public health matter of serious importance? Is this yet another example of assumptions remaining hidden, or is it simply the inability to assimilate new and disruptive concepts? [33].

This review will summarize the increasing body of evidence to show that the unexpected spurts in growth are due to a previously unrecognized infectious agent, specifically one that appears to work via immune modulation. Each outbreak is characterized by synchronous increases in deaths (with condition specificity) [34-42], medical admissions (including case-mix) [6-7,42-44], emergency department (ED) attendances (including case-mix) [45-49], GP referrals (especially for immune sensitive conditions) [50-54] and a wobble in the gender ratio at birth [55].

In the following discussion, the dates for the outbreaks will be referred to with reference to the calendar year in which deaths and medical admissions peak in the UK as a whole, although it is recognized that each outbreak tends to commence earlier in Scotland [37,56], and that at a local area, full spread within a local authority can take one to two years [57-59]. Reference will also be made to new material relating to the spread of these outbreaks across Europe between 2002 and 2013 (see Section 6).

2. HISTORICAL CONTEXT

When seeking to develop a model of real world behavior, the key question should always be, are we missing a key variable? Indeed has the historical literature relating to rising medical admissions missed something of fundamental importance? To address this question Fig. 2 presents the age standardized trend in male and female mortality rates from 2001 to 2013 in England and Wales. As can be seen, the underlying trend line passes through the data points, except for 2002/2003, 2008 and 2102/2013, and females appear to be affected worse than males. I have spoken to a senior actuary from the Life Insurance industry who was aware that these deviations had regularly happened over the course of many years, but was unaware of the reason why they were occurring [60].

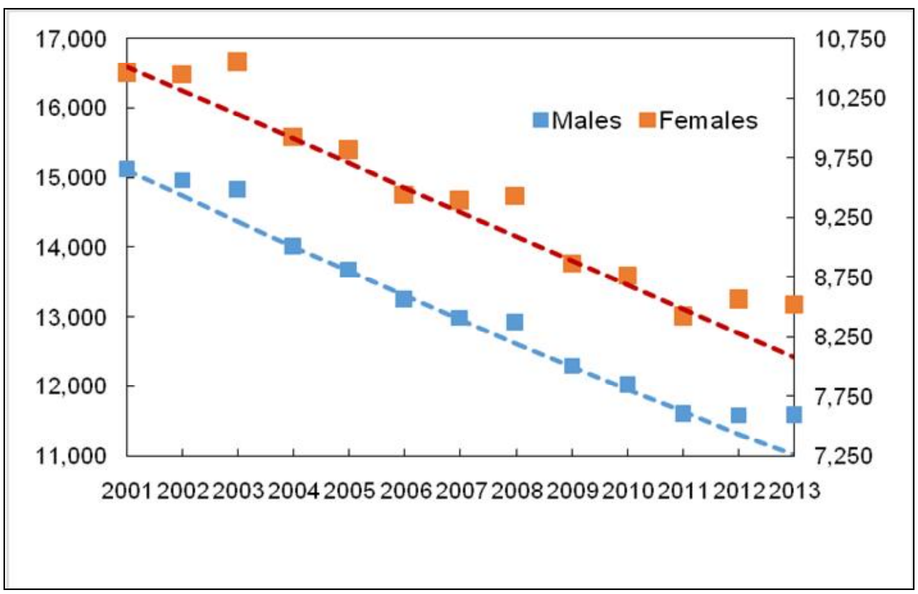

Fig. 2. Trend in age-standardized mortality rates (deaths per million head) in England and Wales

Data is from Office for National Statistics [61] and has been age standardized using the 2013 European Standard Population. The trend line for each gender is from a polynomial curve fit after excluding years when the outbreak has occurred. The size of each square is approximately the 95% CI. Note that females are generally affected worse than males but that this is condition specific, especially for certain cardiac conditions. It is the long-term reduction in death due to cardio-vascular conditions which is largely responsible for the trend down in the age-adjusted mortality rate

From the perspective of the Life Insurance industry, this implies that payments for life insurance policies will be higher than expected in these years. From the perspective of health care, it implies that the downward trend in the mortality rate has been interrupted in a statistically significant manner but for no apparent reason. Something is clearly happening which is powerful enough to make a large impact on all-cause mortality.

The next piece of fundamentally important information is that emergency medical admissions only show unexpected increases at the points at which the age-standardized mortality rate jumps upward, and that both deaths and medical admissions show spatial spread. The literature regarding emergency medical admissions will now be re-examined from this revised viewpoint.

2.1 Information Technology

In the UK, the NHS was established in 1948, but computerized collection of hospital episodes only began in the late 1960's. The collection of data and the quality of the data was patchy, and so in 1980 Edith Körner was asked to chair a committee conducting a full-scale national review of the way information was generated and handled in the NHS. The Körner Committee investigated for four years and produced six major sets of recommendations, all of which were adopted. The committee's work paved the way for a full-scale computerization of the health service. For the next twenty years, the statistical information used to monitor the work of the NHS was known as "Körner Data". Hence it was only until the start of the 1990's that sufficient national data was available to determine how emergency admissions may be behaving over time. Prior to this point data collection was normally conducted by enthusiastic hospital consultants, and hence, only sporadic reports of unexplained increases in medical admissions are available in the literature.

For example, a study at the medical unit of the Glasgow Western Infirmary (Scotland) over the period Feb-68 to Jul-70, shows a clear step-like increase of 16% in attendances and 13% in admissions which initiates around June or July of 1969 [62]. This change was accompanied by a rapid shift away from GP-imitated to self-referral (usually arriving by ambulance), and was not associated with an influenza epidemic. It would seem that it was purely by chance that the consultant was conducting a study at this point in time, and it is highly likely that others were observing such events but never published their observations.

A similar large increase also seems to have occurred in Scotland in late 1984 or early 1985 [1]. A similar surge can be discerned in Scotland and parts of northern England in early 1991 [1,3,63].

2.2 Unexplained Jumps in Medical Admissions

The first instance in which national data was readily available, was a series of three rapid increases observed during the 1990's, namely around 1993, 1996 and 1999. In particular, the 1993 event attracted national attention due to a rapid, large and unexplained increase in medical and mental health admissions across the whole of the UK.

In the financial year 1993/94, emergency admissions for the whole of England had increased by 7 to 13% compared to 1992/93 [64-66]. At the Aintree hospital in Liverpool, there was a 37% increase in medical admissions with an unexpected large increase in the 15 to 44 age group. In nearby Manchester, admissions to one mental health hospital increased by >30% [66]. Parallel increases in medical and mental health admissions were replicated across the whole of England, and medical admissions at the Royal Berkshire Hospital increased unexpectedly by 13%, via an abrupt increase commencing in the middle of March 1993 [67], as did the number of occupied medical beds [68]. The 1993 event was also observed in New Zealand [12,69], and in the USA an unusual increase in emergency department (ED) attendances also commenced in 1993 [70]. Recall that in the USA those who are uninsured resort to the ED as their primary point of contact [71].

Similar events in 1996 and 1999 led to concern that the increase was unsustainable, and created heated debate regarding causes and solutions [1,3-4,10,64-66,72-75], and prompted numerous studies both in the UK and elsewhere [9,65,69,76-78]. An editorial in the British Medical Journal at the end of 2000 noted that these pressures were international in scope and were leading to 'hamster health care' as everyone was running faster to keep up with increasing demand [79]. Historic events such as these, are usually dismissed as having little relevance to present day changes and pressures in the NHS within the UK, and perhaps more widely around the world.

A 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 [80]. However, this assumption contradicted the conclusions from other studies. In the first, research in the USA had demonstrated that acute admission thresholds are maintained despite considerable fluctuation in demand [81], while in the others it was suggested that emergency medical admissions rose in sudden spurts [68,82-83], as per the reports cited above. Indeed, the data presented in the Nuffield Trust report shows evidence for one such spurt of growth at the end of the study period, although the significance of this seemed to have been overlooked within the study, but was noted by others [75].

The sudden increase in emergency department attendances and associated medical admissions in 2012, received much attention, and a report on emergency and urgent care was subsequently published by NHS England [84], along with planning guidance 'Everyone Counts' covering the 2013/14 financial year [85]. Both of these documents imply that the problems are largely to do with the way NHS organizations deliver care, and in a lack of integration between health and social care. While there is a strong case for change in the way services are delivered *per se*, it is curious that neither of these two documents raise a possible link between the increased deaths in 2012 and the parallel increase in unscheduled care.

3. RED HERRINGS

A red herring is a figurative expression referring to a logical fallacy in which a clue or piece of information is misleading, or distracting from the actual question or issue. This section will discuss several red herrings that have distracted researchers away from the underlying issues.

3.1 The Ageing Population

As a rule-of-thumb, for the more medical conditions, the underlying demographic growth can be multiplied by a factor of two to three to get an approximation for longer term growth; while that of the more surgical interventions tends to be closer to the demographic trend.

In the UK it has become an everyday occurrence to hear a politician or newspaper article declare that it is the 'ageing' population that is the cause of the financial pressures in the NHS. Hence we need to establish if the commonly held notion of the ageing population (population demographic change), actually contributes to rapid growth in health service demand and financial pressures.

Economists have known for many years that the ageing population *per se* only contributes around 1.5% per annum growth [86]. Studies on the cost of future health care always adjust for the fact that it is not age *per se* that leads to higher cost, but the number of years to the end of life [87]. One study in Sweden has shown that the age of first admission has risen in line with rising life expectancy [88]. Other studies have shown that the majority of a person's life time utilization of acute care occurs in the last year of life, irrespective of age at death [89-91].

In confirmation, a number of comprehensive national and international reviews have concluded that demographic change only plays a minor role in the overall increase in medical admissions [1,12-15]. A study in Scotland found that demographic change could only account for one-tenth of the observed increase in admissions for all ages, and around one-third of the observed increase for ages over 65 [14]. A study covering the population of the former Avon health authority found a real rise of 1.4% p.a. over the period 1989/90 to 1997/98, of which only 0.6% p.a. could be explained by demography [2]. Only 40% of the observed rise in emergency admissions in England between 2004 and 2009 could likewise be explained by demographic change [80].

For most inpatient specialties, population growth will only yield a forecast for future admissions which shows roughly linear growth over a ten year interval. This demographic-based growth typically ranges from less than 0.5% per annum for ENT, oral surgery, gynaecology, etc through to 1.0 to 1.5% per annum for rheumatology, urology, thoracic medicine, cardiology and general & elderly medicine. The all specialty average in England is just above 1% per annum. End of life itself is a major factor in the number of healthcare interventions, and there is a 10-fold increase from five years prior to decease to the last year of life [92]. Hence demographic change only sets a minimum baseline increase and does little to explain the highly erratic nature of the long-term time series or the extent of the increase.

Table 1 investigates this issue in more detail by looking at the diagnoses showing the highest numerical growth in admissions in England between 2001/02 and 2011/12. Only diagnoses with greater than a net increase of 15,000 admissions are shown in Table 1, and this limited set of diagnoses accounts for 1.25 million additional admissions (over and above demographic growth) during the 10 year period. As can be seen, over the ten year period, demographic change only contributed to between 7% and 17% growth, i.e. between 0.7% and 1.7% per annum growth. However, non-demographic sources of growth accounted for anywhere between 16% and 70% (median 35%) growth. Also note that the non-demographic growth is *not* consistently associated with diagnoses having a high proportion of elderly persons. The unexplained increase in the diagnoses associated with injury, wounds and fracture, has been proposed to be due to the clumsiness which arises when a person is feeling unwell, i.e. implies additional periods of infection over and above that normally expected.

A final feature of demographic-based growth is illustrated in Fig. 3, namely, that demographic-based growth projections only show continuous (smooth) growth trajectories. This fact needs to be kept in mind, since later sections of this review will give numerous examples of discontinuous growth trajectories, all of which commence around the time that the proposed infectious outbreak has its commencement.

It is plainly evident that the so-called ageing population *per se* has very little to do with growth in admissions or cost pressures. One suspects that the ageing population has become a 'sound bite' used by politicians to 'simplify' a complex issue. Indeed the danger of 'sound bite' health policy is that it leads to entirely inappropriate initiatives to solve 'the problem'. For example, hospitals in England were being given financial incentives to place (elderly) patients on the Liverpool Care Pathway (LCP). The LCP is only ever intended for severely ill (mainly cancer) patients in the very last days of life and involves medically approved withdrawal of food, and sometimes drink, to hasten decease. The financial incentives led to totally inappropriate use of the LCP directed at elderly persons, some of whom may have survived with proper care [93].

However, at the same time, it is evident that the reason for the increased medical admissions lies in increased elderly admissions, and that the rate of increase increases with age, i.e. estimated future admissions always undershoot the actual value. Indeed the rate of admission per head shows an almost linear increase over time, and the slope of this increase rises with age. For example, in Scotland there were two emergency admissions per ten head of population for those over the age of 85 in 1981 and this had risen in a straight line manner to 4.2 admissions per ten head in 2001 [14].

Such unexplained growth in admissions for medical conditions has especially been noted for 'signs and symptoms', i.e. ICD diagnoses beginning with 'R' in Table 1, i.e. something is acting in the background which leads to diagnostic ambiguity or admission for a vague and difficult to define illness [7].

In Scotland the fastest growing diagnosis among the elderly is for the ill-defined diagnosis 'signs & symptoms' [14,72]. In a similar vein the highest increase in surgical admissions in Exeter (UK) was for non-specific abdominal pain followed by constipation [94]. Another study investigating admission rates in England showed that the rates for ill-defined conditions had doubled for age groups over 65 years during the nine year period 1995/96 to 2003/04 [95]. These are non-specific 'admit to diagnose' type conditions.

In conclusion, demographic change *per se* has little to do with the large increase in medical admissions seen for many years and alternative explanations are required. However an additional age-specific effect appears to be driving the increase (See Section 7.7).

3.2 Same Day Stay Admissions

Same day stay or zero-day stay admissions are patients who are admitted (mainly for diagnosis and some rapid treatment), and then discharged on the same day. These 'admissions' are usually associated with the introduction of medical assessment units (MAUs). MAUs are a desirable feature of rapid access medicine where a GP may require an expert opinion in order to avoid an otherwise unnecessary hospital admission (involving one or more overnight stays) [96-97].

Table 1. Diagnoses with highest numerical increase in admissions (England)

ICD code	Primary diagnosis	Increase 2001/02 to 2011/12 Net increase	Demo-graphic	Non-demo graphic†	Proportion aged 75+ (%)
A08	Viral and other intestinal infections	15,829	11%	40%	14%
A40/41	Septicemia	28,017	13%	55%	43%
B34	Viral infection of unspecified site	22,532	11%	30%	2%
E87	Fluid-electrolyte & acid-base balance	21,980	13%	65%	51%
F10	Mental/behavioral disorders - alcohol	28,393	7%	44%	3%
I26	Pulmonary embolism	15,086	12%	37%	37%
I48	Atrial fibrillation and flutter	26,072	13%	20%	44%
I63	Cerebral infarction	54,855	14%	47%	61%
I95	Hypotension	16,720	14%	55%	72%
J03	Acute tonsillitis	25,591	7%	41%	0%
J18	Pneumonia organism unspecified	170,977	14%	55%	60%
J22	Acute lower respiratory infection	21,243	13%	16%	46%
J44	Chronic obstructive pulmonary disease	41,746	13%	22%	46%
J69	Pneumonitis due to solids and liquids	18,738	14%	67%	62%
K52	Non-infective gastroenteritis/colitis	38,429	10%	23%	20%
K80	Cholelithiasis	25,588	10%	18%	22%
K92	Other diseases of digestive system	22,394	11%	18%	33%
L03	Cellulitis	31,678	12%	34%	37%
M16	Coxarthrosis [arthrosis of hip]	20,289	12%	27%	33%
M17	Gonarthrosis [arthrosis of knee]	31,156	12%	29%	28%
N17	Acute renal failure	42,181	14%	70%	62%
N20	Calculus of kidney and ureter	16,153	9%	22%	8%
N39	Other disorders of urinary system	134,163	14%	47%	58%
R07	Pain in throat and chest	96,912	11%	29%	22%
R10	Abdominal and pelvic pain	52,510	8%	16%	10%
R41	Cognitive function and awareness	19,379	14%	43%	67%
R51	Headache	26,589	8%	37%	10%
R54	Senility	36,874	17%	48%	87%
R55	Syncope and collapse	33,861	12%	29%	50%
S00	Superficial injury of head	28,530	12%	64%	43%
S01	Open wound of head	30,558	12%	48%	40%
S72	Fracture of femur	20,963	16%	19%	77%
T39	Poison by non-opioid analgesic, etc	19,284	8%	33%	3%
T81	Complications of procedures	22,527	9%	30%	16%

Data is from Hospital Episode Statistics (HES). Demographic growth has been calculated based on admissions in 2012/13 by five year age band per matching five year population from the Office for National Statistics (ONS). Expected admissions were then calculated in previous years using ONS population data for those years. Admissions include both elective and emergency admissions. The 'net increase' in admissions has been adjusted for the increase in 'day case' admissions, which may have been artefacts of the introduction of Payment by Results [21], and also excludes the contribution from demographic growth. (†) Minimum possible increase. Some non-demographic growth may have arisen following the introduction of the four hour target in the emergency department in 2002 [24-28]. This has been partly compensated for by calculating % increase relative to 2011/12 rather than 2001/02

Prior to 1990 in Scotland, these admissions remained at relatively the same proportion of total emergency admissions. After 1990 they began to rise with inflections leading to a higher rate of increase in 1993, and at the end of 1996. Hence between 1990 and 1997 a massive 90% of the total increase in Scotland was due to short stay admissions [98]. A similar increase in same day emergency admissions has been observed in Australia where there was a 46% increase in zero day admissions in the six years between 1994 and 1999, and this accounted for over 95% of the total increase in emergency medical admissions [99]. It was noted that the main medical zero day stay admissions were for chest pain, abdominal pain, injuries, digestive diseases, poisoning, urinary stones and headache.

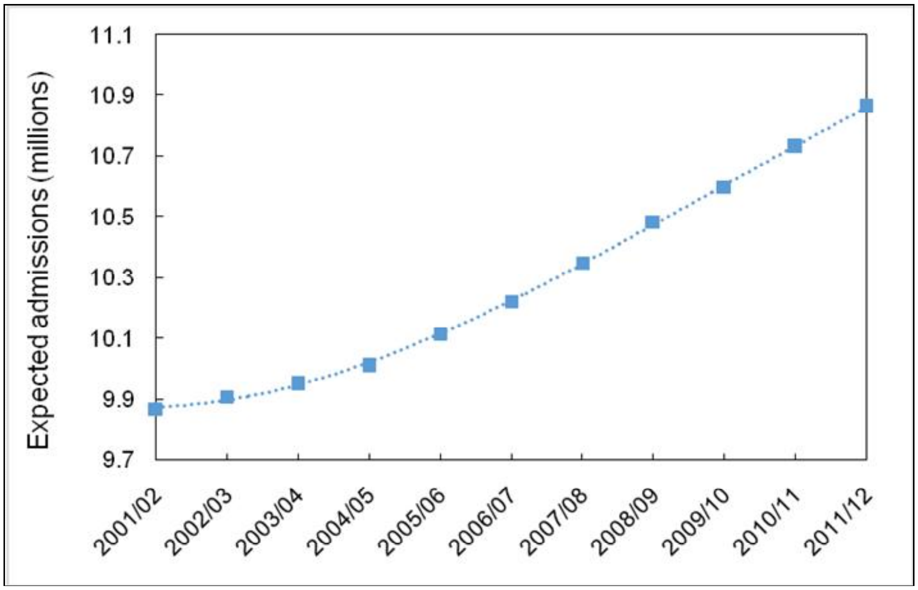

Fig. 3. Expected growth in admissions due to demographic change in England
Data is for the 680 diagnoses showing a net increase in admissions over and above demography

One study in England over the period 1989/90 to 2005/06, demonstrated that overnight stay medical admissions increase by 33% which is roughly 2.4% per annum or about double that expected from demographic change. However, in a nine year period to 2000/01, zero day stay admissions had doubled, which is roughly 10% per annum growth. Beyond 2002/03, zero day stay admissions show unprecedented growth due to the reclassification of A&E attendances as an 'emergency admission', arising as an artefact of the A&E four hour target. In a similar way Trauma & Orthopedic overnight stay emergency admissions only grow by 3.8% over a 16 year period to 2005/06 (which is far less than demographic growth), while zero day stay admissions grew by 107% over the same time period [82].

In England, the trends were markedly altered by the introduction of the four hour target for a maximum stay in the emergency department. This target was announced in 2001 with 98% of patients seen within four hours to be achieved by 2004 [100]. The Labour government of Tony Blair saw the target as a major policy initiative and performance was rigorously enforced. In many ways the introduction of the target accelerated the introduction of emergency assessment units (EAU), with the added advantage that if the patient was 'admitted' direct to the EAU they were no longer subject to the target [24-28]. Hence the vast growth in same day emergency admissions which commenced in 2002/03 [101-102]. The proportion of zero day emergency admissions then became highly variable between hospitals [103-104], and growth in England far exceeded that in the other countries in the Union (where the target was not introduced until years later) [105]. Between the years 2002 and 2006, some 450,000 extra zero day admissions accounted for 43%, 50%, 74% and 86% of growth in Medicine, Surgery, specialty Accident & Emergency and Pediatrics respectively [105]. However by around 2007 this effect had reached saturation. The net result of these changes was to partly obscure the 2002/2003 outbreak. This outbreak also occurred during a period of massive growth in NHS funding, and hence did not attract prolonged attention [7].

We must therefore ask the fundamental question, are the zero day stay emergency admissions simply a part of the natural continuum of ambulatory care, i.e. the equivalent to an urgent outpatient appointment or an ED 'type' attendance? If viewed in this light, the large apparent increase in zero day stay 'emergency admissions' becomes a much smaller increase in outpatient first or ED attendance, and the residual increase in emergency admission for the majority of diagnoses becomes much closer to that arising from simple demography. In England, the presence of large numbers of zero day stay admissions in the emergency data set does create serious problems for the evaluation of average length of stay [23], and for the correct determination of rates of hospital admission. Research in this area must treat zero day stay activity as a separate entity [106].

Higher numbers of short stay admissions are however an underlying longer term phenomenon, and cannot explain the step-like behavior seen in the time series for medical emergency admissions and associated deaths.

3.3 Readmissions

Readmissions after an emergency admission, and the number of episodes per person, have been rising for many years in both the UK and the US [2,80,107-108]. Re-admission rates have increased year on year since 1981, and it is the oldest age groups that have experienced the highest (non-linear) increase. The highest rate of increase in re-admission for those aged over 80 is for 'signs and symptoms', while the incidence of re-admission for heart disease has been declining and that for respiratory infections has remained a simple linear increase [14]. Rates are highest in Nephrology, Hematology, Poisoning and Respiratory Medicine [107], and readmission in the UK appears to be mainly related to long-term or chronic (physical or mental health) conditions, (re-admission rate is in brackets), such as COPD (24%), angina pectoris (13%), acute myocardial infarction (12%), and atrial fibrillation & flutter (11%) [109]. A similar pattern is found in the USA, and a 2010 study listed 30 conditions with all-age 30-day readmission rates in excess of 20%. 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 [110].

Readmission rates are also known to be higher in males, and increase with increasing age, deprivation, and length of stay, higher number of co-morbidities and after primary admission for COPD/Asthma or heart failure [108,111]. They are higher in those hospitals with a lower in-hospital mortality rate, i.e. patients discharged alive are free to readmit [112]. Although the re-admission rates are highest among the most deprived, the rate of increase over time appears to be independent of high or low deprivation groups [109].

Patients who are readmitted, have a higher in-hospital mortality rate [108] consistent with a chronic condition. Multi-morbidity and age 75+ are strong predictors of readmission [111]. A recent study has demonstrated highest growth in admissions is occurring among age 75+ in around 100 primary diagnoses usually associated with multiple morbidities [22]. Growth was highest around the times of the proposed disease outbreaks, suggesting that readmissions are a symptom of increasing comorbidity rather than a cause.

3.4 Spatiotemporal Spread

Spatiotemporal spread of deaths and medical admissions which is independent of the location of acute hospitals, is strong evidence for the spread of an infectious agent. However if ignored it acts as a confounding factor in attempts to understand the problem.

While there is evidence for spread at national, state and regional level, the clearest evidence for infectious spread comes from recent studies using small-area aggregates of around 7,000 population as defined by what are called Mid Super Output Areas (MSOA). A MSOA contains sufficient medical admissions to demonstrate statistically significant changes in admission. Three studies have identified slow spread of a presumed infectious agent leading to very large increases in medical admissions between MSOA in North East Essex, Wigan (near Manchester) and Berkshire [57-59], all of which are totally independent of hospital characteristics. It is the kinetics of the infectious spread which determines the shape of the apparent cycle seen across the whole of England which will be illustrated in later sections. As a result of this spread, different shaped profiles can be observed in Queensland (Australia), Canada and the USA [113-115]. Is there evidence to suggest that spatiotemporal factors were at work in the earlier studies investigating growth in medical admissions?

For example, we now know that in the 1993 outbreak, deaths spread across the local authority areas of Scotland between Dec-92 to Jun-94 [56], however, spread at small area level probably commenced in early 1992. Such differences in timing can indeed be seen in the data for admissions via the emergency department in Sheffield, Hull and Scarborough [3]. My own re-analysis of regional data following the 1993 outbreak suggested that spatial spread was involved [67].

The Nuffield Trust study of emergency admissions between 2004 and 2009 in England [80] caught the end of the 2003 outbreak and the middle of the 2008 outbreak. This study categorized hospitals into regions and noted unexplained patterns of change which were attributed to large changes in the way in which services were delivered. Primary Care Organizations (PCOs) displayed an equally curious spread of increases during the 2008 outbreak. In this respect the 2008 outbreak occurred in Scottish local authorities between Oct-06 and Mar-09 [56], while spread of the 2008 outbreak across Europe occurred between Mar-05 and Aug-08 (see Table S1 and Section 6).

The differences in the magnitude of PCO costs emanating out of the 2003 and 2008 outbreaks was also seen as evidence for spatial spread of an infectious agent [114].

It would seem that spatiotemporal issues have been consistently ignored or misinterpreted, and this largely explains why contributory rather than causative factors became the 'de facto' explanation for the increase in emergency admissions (next section).

3.5 Causative versus Contributory Factors

In the absence of an acknowledgement of infectious spatial spread, researchers will be tempted to erroneously attribute causation to contributory factors.

All of the supposedly causative factors such as, supply-induced demand, an ageing population, the elderly living alone, conservative GP and hospital consultant behavior, health care consumerism, rapid advances in technology and increasing complexity of treatable conditions, the failure of health care organizations to 'manage' demand, inappropriate admissions, lack of integration between health and social care [5-18], have never been proven to be causative in that all show roughly steady growth over time and cannot explain the step-like increases in death and medical admissions which sweep across the UK and Europe (see Section 6).

4. A CONCEPTUAL FRAMEWORK

The following section provides a conceptual framework to the research and describes the wider context of the outbreaks. Advances in immunology over the past decade have yielded a workable basis for a medically valid context. Firstly, the step-like increase in deaths, admissions and costs implies a permanent infection (called a persistent infection), such as observed in HIV/AIDS, hepatitis, tuberculosis, etc, as opposed to the more familiar spike-like infectious events seen for influenza, SARS, measles, etc. This does not deny the fact that spike-like infectious events can leave lasting health impairments. For example, Reye's syndrome and Influenza B and cardiomyopathy for Influenza A (H1N1) [116-117]. However, it is suggested that it is more probable that the agent is persistent given the large number of persons affected, and the extended time scale during which the effects are observed.

The key features of the infectious outbreaks are as follows:

1) Spatio-temporal spread of the infectious agent

   a) Implies MAUP (modifiable areal unit problem) effects for geographic areas of different shape and/or size, hence, different views of the same event from say the perspective of a hospital and its catchment area, and local authority areas which may be serviced by one or more hospitals. By extrapolation different views at regional, state and national level.
   b) Implies areal granularity arising from unique geography, population age, gender, ethnic and socio-economic structures, hence, disproportionate effects upon activity and cost between PCO locations.
   c) Implies areas that are affected early and other which are affected later in the outbreak.

2) Age and gender specificity

   a) Differential immune functional responses between the genders.
   b) Changes in immune function with age, called 'inflammaging'.
   c) The opportunity for what is called 'original antigenic sin', i.e. saw-tooth patterns in the magnitude of the infectious severity with age arising out of sequential exposure to different strains of the same infectious agent.
   d) The effect of 'original antigenic sin' upon single-year-of-age patterns implies that

traditional use of five-year age bands for the calculation of age-adjusted morbidity and mortality may yield flawed results.

3) A limited range of diagnoses which are particularly affected

   a) Certain infectious, inflammatory (including granuloma and specific cancers) and autoimmune-based conditions/diseases, will be more sensitive to the effects of an immune modulating agent than others.
   b) By definition a range of diagnoses/conditions which are *not* affected.
   c) A range of by-stander conditions which could be affected, for example, illness and general malaise can lead to an increase in clumsiness and hence an increase in accidents, falls and fractures Table 1.

4) Diagnostic ambiguity

   a) Subtle changes in disease severity and rapidity, influenced by immune modulation, resulting in a mixed cause/effect diagnostic conundrum. For example, a genetic predisposition to a certain type of cancer, but whose speed of development and perhaps initiation is enhanced by immune modulation.
   b) The absence of a framework that allows clinicians the opportunity of separating cause and effect.
   c) The situation made worse by an ageing western population where natural 'inflammaging' is an enabling component.

5) A disease time-cascade

   a) Particular diseases/conditions sensitive to immune modulation will display a characteristic time-lag before the full disease progression is evident.
   b) The lag could range from a few days to several years.
   c) The lag will be modified by the single-year-of-age patterns arising from 'original antigenic sin'.

Having outlined the scope, the detail will now be discussed.

5. CHARACTERISTICS OF THE OUTBREAKS

I recall telephoning the editor of the British Journal of Healthcare Management in early December of 2008 to discuss the possibility of a paper exploring the evidence for a new infectious-like event affecting emergency admissions. This was eventually published as a four-part series commencing in April 2009 exploring trends in emergency admissions, cycles in emergency admissions, and the effects upon hospital bed requirements and costs [82-83,118-120]. Six years of research later, and the evidence for these outbreaks has been substantially accumulating - summarized in Table 2.

The proposal that the actual agent may be a ubiquitous herpes virus, with powerful immune modulating properties, called cytomegalovirus (CMV), has been summarized elsewhere [7,40-42,143-145]. The causative agent is not the focus of this review, and the reader is advised to consult this additional material to gain further insight into the immunological and hospital case studies relating to CMV infection in the supposedly immune competent patient. While CMV is only a potential candidate, it however does provide a useful model for the type of immune modulating agent that is likely to instigate the events outlined in this review. Key aspects will now be discussed in further detail.

5.1 Deaths

In 2012 deaths across the UK suddenly and unexpectedly increased with at least 45,000 'excess' deaths spread across 2012 and 2013 – the equivalent of a very large influenza epidemic. This was a repeat of similar events which peaked in 2003 and 2008. No official explanation has ever been offered. However, infectious-like geographic spread was clearly evident [34-38]. Indeed the missing element in the majority of studies on rising medical admissions is the fact that admissions only surge when deaths show a spike.

Table 2. Key characteristics of the infectious outbreaks

Characteristic	Specific comments and references
Countries affected	
All parts of the United Kingdom	Various studies demonstrating the same event with multiple consequences in England, Northern Ireland, Scotland and Wales [7,34-39,50,57-58,121].
Other Western countries	Similar events documented in Australia [113,120], Canada [113,115], New Zealand [122-123] and USA [115]. Outbreaks in New Zealand appear to be less prominent than elsewhere. Review of other studies suggest outbreaks in the Irish Republic and Greece [7]. Unpublished studies of trends in medical admissions show similar events in Austria, Estonia and Switzerland. The outbreaks responsible for these increases across Europe are confirmed in this review using the associated increase in deaths. See Section 6.
Only Western countries?	If CMV is the causative agent, different countries are known to have a predominance of different strains [42]. This aspect requires clarifying research.
Spatio-temporal spread	
Spatio-temporal spread	As expected of a genuine infectious outbreak, both the spread of deaths, GP referral for an outpatient attendance and emergency medical admissions show time-space (spatio-temporal) spread and granularity [34-35, 37-38, 56-59]. Small area spread within a local authority takes 12 to 18 months while spread across the entire UK takes 2 to 3 years [37-38]. Similar time-space effects can be observed with English PCO costs [114,124] and bed occupancy in hospitals [125]. Spread across the whole of Europe takes mostly 24 months for the 2002 and 2012 outbreaks, but took 36 months for the 2008 outbreak. See Section 6.
North to south movement	Several studies have implicated a general north to south movement [67,124], however, the most accurate evidence comes from a study of the increase in deaths in Scotland which shows earlier initiation than seen in England [37]. This does not apply to every location in Scotland but earlier initiation is more prevalent [56]. A potential link with vitamin D levels has been proposed [7,59]. However, the outbreak in Europe shows no particular relationship with latitude. See Section 5.6 for more detail.
Month of initiation	Three studies covering small-area infectious spread following the 2008 and 2012 outbreaks have shown that spread between small areas occurs more frequently during the winter months and reaches a minimum in August [57-59]. This pattern follows the levels of vitamin D in the blood. Similar conclusions have been reached for all outbreaks since 1993 in Scotland [56]. A similar month of year pattern also applies across Europe (See Section 6).
Specificity of the effects	
Specialty and condition specificity	A number of medical specialties show an increase in admissions during the outbreak, and there is an overspill into medical conditions admitted in other specialties, and also to particular diagnoses in mental health [7,31,43-44,124]. Within this general medical focus there are certain conditions which are affected more than others, and a cluster of 90 medical diagnoses are especially linked to high growth in elderly (age >70) admissions [22]. Certain cancers also appear sensitive to the disruptive effects of these outbreaks/events [126]
Age specificity	One study in Northern Ireland for infants under one year of age demonstrated that the very young appear to be affected by the outbreaks [7], due to the fact that the very young have a specific CD4+ immune deficiency which resolves with age. The effects against medical admissions are single-year-of-age specific [57-59], an effect also observed in Australia for the 2008 outbreak (unpublished). The up and down movement over time in the number of elderly admissions arising from

Characteristic	Specific comments and references
	these events leads to very high volatility in elderly costs [127]. Deaths in England and Wales after the 2012 outbreak also show single-year-of-age specificity [39].
Gender specificity	During the outbreak there is a higher proportion of female admissions and deaths [7]. However the gender specificity appears to have an additional condition-based component [128]. Growth in PCO expenditure following the 2008 event appears to be higher in those regions where there is a higher ratio of elderly females [124].
Transferable case mix	For a genuine infectious event the case mix must be the same in different countries. For the 2008 outbreak the case mix for England [19-20,31] gives similar results in Northern Ireland [44] and Canada [114]. A preliminary study in Australia gave a similar case mix associated with the 2008 outbreak in Sydney [120].
A disease time-cascade	If the condition were immune-based then there would be time-based effects against different conditions. Such disease time-cascades have been demonstrated following the 2008 [57] and 2012 outbreaks [58-59,129], and in Australia following the 2008 outbreak (unpublished). Of particular interest is the fact that emergency admissions in Oncology appear to peak after one year [130], while admissions for the more aggressive forms of tuberculosis peak after three years [131]. Admissions for allergy peak around one year later [132]. GP referral to outpatients also demonstrates a specialty-specific time cascade [51], and there appears to be a time-cascade in dermatology conditions following the 2008 event [52]. In the USA, the ratio of female to male costs for a range of long-term conditions (including cancers), show lagged cycles which appear to emanate out of these outbreaks in that country [133]. A time-cascade in deaths and admissions has been observed for particular conditions/diagnose following the 2008 and 2012 outbreaks [57-59,129].
Aspects of health care affected	
Emergency department (ED) attendances	Analysis of a long time series for ED attendances in England shows the typical time-based undulations arising from these outbreaks [45-47]. During the 2012 event the attending case-mix shows an abrupt shift to more serious medical conditions with infectious diseases showing the greatest increase [29]. Growth in A&E attendance is largely driven by those who progress to be admitted [30,45-46] and more so for the elderly [45-46]. However, there is additional age-specificity with a marked increase in attendance for those aged 50-59 following the 2008 event [49]. There are consequent impacts on ambulance call-outs [33].
Deaths	Deaths show a characteristic increase shortly after the onset of each outbreak [34-37]. Deaths are age, gender and condition specific [34,134-136]. Persons suffering from neurodegenerative diseases show the highest percentage increase in deaths during the outbreaks [40]. Respiratory deaths also increase [41] as do vascular system [137] and digestive deaths (in preparation).The age-specificity leads to a saw-tooth pattern in single-year-of-age admission rates and deaths [39,59]. Such a saw tooth pattern is indicative of the immune phenomena called 'original antigenic sin' [138]. Increased deaths spread across the UK over a period of two years in an infectious-like manner [35-38,56-59]. Deaths will be a lagging rather than leading indicator for the outbreaks.
GP referrals	GP referrals appear to show a more variable response to these outbreaks. In the UK, the 2008 event led to a particularly large increase compared to the 2003 and 2012 events [50-51,131]. GP referrals show spatial spread, and there is evidence that there is a time-based cascade regarding which specialties are affected earliest [50-51]. These effects upon GP referral then have knock-on effects to the rate of follow-up appointments in several specialties [53]. Increase in outpatient attendance for the 2012 event is

Characteristic	Specific comments and references
	greatest for those conditions and specialties which are immune sensitive [54].
Occupied hospital beds	Bed occupancy in the UK, Australia and Canada rises in the medical group of specialties after each outbreak [113,120]. A typical decline in bed occupancy in the interval before the next outbreak usually lures hospital managers into closing beds under the false assumption that 'efficiency' measures are responsible for the decline [118]. The resulting chaos when the outbreak eventually arrives is somewhat predictable and results in queues in the ED and cancelled elective surgery [134,139].
Gender ratio at birth	Each outbreak initiates the start of a cycle in gender ratio at birth. More males are born at the start of the cycle and more females toward the end [55]. Only a few agents such as specific types of nuclear radiation (i.e. the aftermath of Chernobyl) or temperature patterns are capable of shifting the gender ratio toward males [55].
Financial and cost pressures	Each outbreak initiates a cycle of deficit/surplus which is seen at a national and local level [140-141]. The picture seen at national level is a composite of local timing and extent of impact. Some localities therefore experience far greater cost pressures [57,114,140-141], including pressure on hospital beds [113,125]. There are knock-on effects to the apparent volatility of admissions in different specialties [142]
Historical evidence	
Historical evidence	Evidence for a far longer time-series of these outbreaks can be discerned in the literature [see 7,129]. However this evidence was misinterpreted as 'solely' arising from deficiencies in the process of acute, primary and social care. Data from the USA suggests the outbreaks go back to at least the 1960's [115]. A recent study on monthly deaths in England and Wales suggests that the outbreaks have been present at least from the 1950's [38].

While failure on behalf of health care processes can be argued to increase deaths in a general way, this fails to explain the large-scale epidemic-like outbreaks of death in the UK which peaked in 2003, 2008 and 2012/2013 and at dates prior to this [38]. Typically 20,000 to 30,000 people appear to die in these outbreaks, and this has been illustrated in Fig. 2 (effect on age-standardized mortality) and Fig. 4 where total deaths are often spread across two years. The cluster of three outbreaks in the 1990's can be seen as a large peak in 1993 followed by a series of high years between 1995 and 1999. Indeed a similar effect against age standardized mortality (as in Fig. 2), has been demonstrated in Scotland going back to the 1990's [137].This series of high years is a result of spatial spread across the whole of the UK, and the suggestion is that some of these outbreaks may have been more regional in nature. For example, little evidence for the 1999 outbreak in Berkshire [82]. Note that the 2008 outbreak had a relatively weaker effect on deaths and admissions in the UK [34], and in Europe (see Section 6).

Analysis of the 2012 outbreak using monthly data at local authority (LA) level, has allowed the exact point for the onset of the step-like increase in deaths for each LA to be identified, and an 'average' figure of 45,000 deaths for England & Wales (excluding Northern Ireland and Scotland), is thereby increased to a 'true' figure of probably in excess of 60,000 extra deaths [38]. Deaths are condition, gender and age specific [34,40-41,64-65,135-137], and show clear single-year-of-age patterns expected from antigenic original sin [39], i.e. the immune effects of repeated exposure of a population to different strains of the same infectious agent [138]. We are clearly dealing with a huge infectious event of major public health importance.

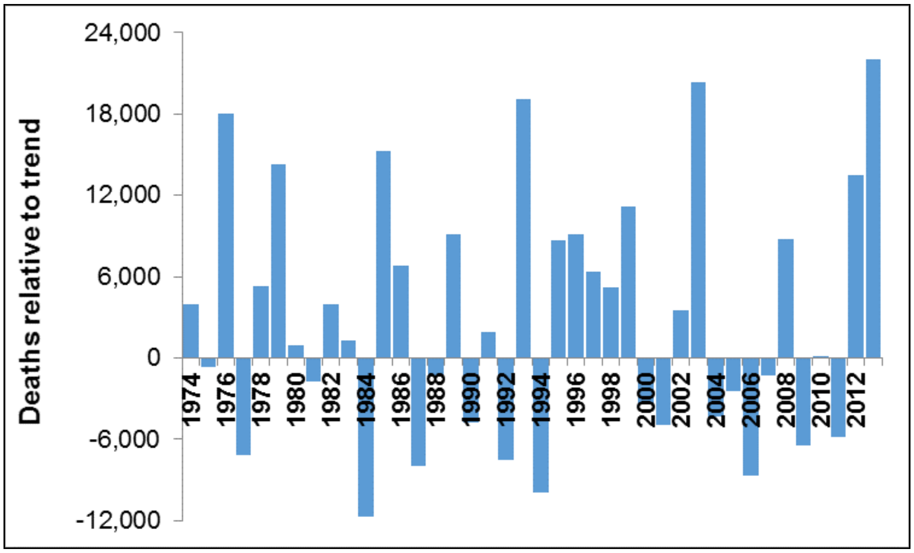

Fig. 4. A time-series of annual deaths in the UK

Deaths are for the entire UK and are from the Office for National Statistics (ONS). Trend is from a polynomial fit excluding peak years. The peak in 2013 appears to relate to later spread in parts of Northern Ireland and England

5.2 Medical Admissions

As discussed in Section 2.2 at a local level, these spurts show as a step-like change in medical admissions. A step change is an abrupt increase in rates of admission which remains indefinitely or for an extended period of time. To illustrate these points Fig. 5 shows a time series of medical admissions as a proportion of total overnight admissions in England. The arrows mark the points of onset of the outbreaks which are evidenced in the following financial year as a step-up which is then followed by a cycle leading to the next step-up. For data covering the whole of England this 'cycle' is a MAUP-induced artifact of small-area infectious spread across the whole of the UK which takes around two years for complete spread to occur [34-38,50,57-59]. This extended duration of spread has been proposed to be due to relative difficulty of transmission of the agent mixed with local mini-epidemics arising from a respiratory phase of transmission [41]. Attendance at GP surgeries may act to facilitate local spread [57].

The popular misconception that increased emergency admissions is an acute threshold to admission issue [80] is no longer tenable [50]. Hospital management simply do not interfere in the clinical decisions surrounding emergency admissions. While there is some leeway surrounding elective admission, I have yet to come across any hospital manager who claims to have *directly* interfered with the non-elective clinical process other than by process re-design (usually to reduce admissions), or the introduction of a medical assessment unit. The increase in medical admissions only occurs when deaths show the epidemic-like spikes and are confined to particular medical conditions with associated age and gender specificity [19-20,39-43]. These conditions also appear to be associated with growth in bed occupancy. Both the increase in admissions and deaths cluster around conditions where CMV is known to exert its clinical effects [145]. Further work is required to determine if this is the primary agent.

One of the more intriguing consequences of these outbreaks is an associated increase in the ratio of Finished Consultant Episodes (FCE) per Spell [129]. An FCE is the time spent under the care of a single consultant, while the Spell is the duration of the entire admission. Fig. 6 shows an increase in the ratio of FCE:Spell over time, which is unique to the more medical specialties and is indicative of the increasing complexity implied with the links to multi-morbidity [22,146].

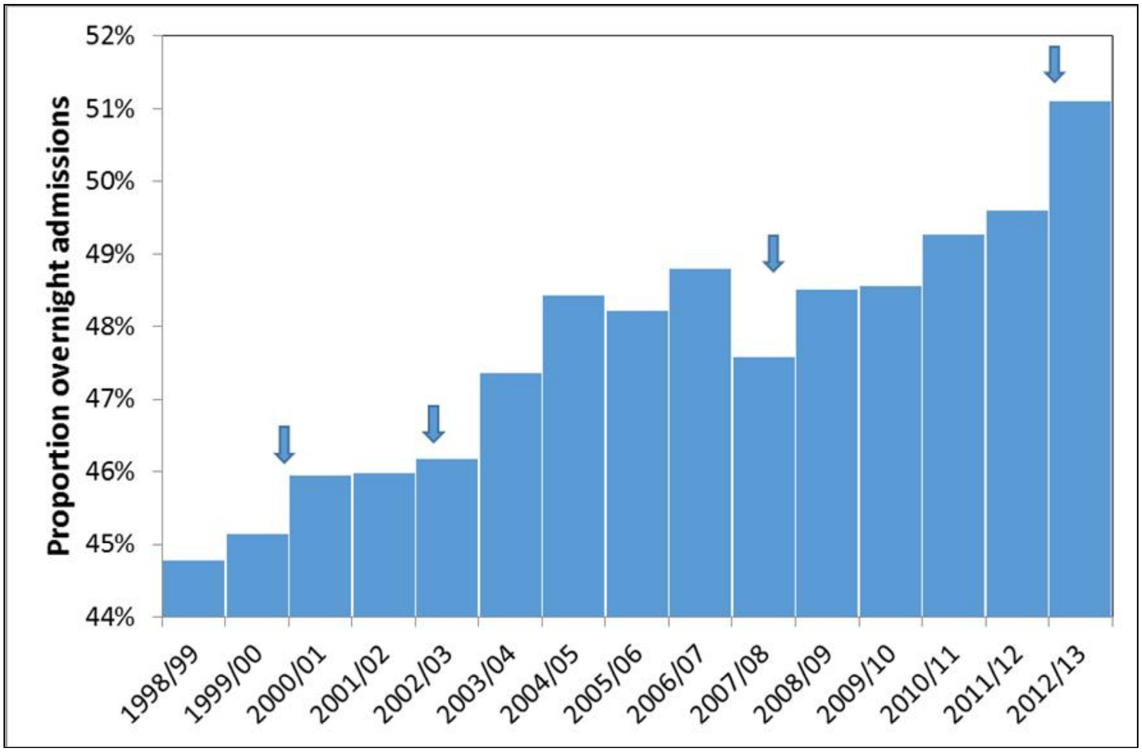

Fig. 5. Medical specialties share of total adult overnight admissions

Data in Figs. 2 to 5 covers English residents and is from Hospital Episode Statistics (HES) extracted from the NHS Health & Social Care Information website. Excludes Paediatrics, Maternity and Mental Health as specialties, also excludes admissions into specialty 'Accident & Emergency' as potential emergency department attendances. Day case elective admissions are also excluded. The arrows are placed in an attempt to indicate the point in the financial year that the outbreak commenced in England

It is interesting to note that around the time of the 1993 event/outbreak, a specific increase in the ratio of FCE per Spell was also noted to occur in the Avon region. Re-appraisal of the data presented by Morgan et al. [2] reveals greater than a 35% increase in the slope of the trend line for FCEs either side of 1993/94, a step-like increase in persons admitted and an intermediate increase in admissions. Interestingly, the data also shows evidence for the second of these events which occurred in 1996. Analysis of this second event is limited by the fact that the data ends in 1997/98. It can also be seen that the 1993 event did not reach the Avon region until the later part of the 1993/94 financial year, i.e. the issue of spatial spread. The specific and large increase in FCE noted above is suggestive of an increase in complexity, and similar increases in complexity (and complications) have been noted to occur in both Canada and the USA at times when these events appear to occur in these countries [147-151], and has been discussed in a recent review [7].

This ability to alter the course of different diseases has been demonstrated using data for the USA where particular cancers show a cycle over time whereas other do not [126]. The cycle in medical admissions seen for the whole of the USA [115] is simply an expression of MAUP-based trends arising from the fundamental small area spread over a very large geography. Higher sensitivity to the outbreaks is typically associated with the elderly [8,127], and this is consistent with the enabling effects of 'immunosenescence' and 'inflammaging' in ageing [152-154].

5.3 Ratio of Female Admissions

A further sub-set of condition-specificity is a general predisposition to greater effects against females [7], and which even extends to unique selection against females in the womb [55]. This is illustrated in Fig. 7. While autoimmune diseases are known to have a general female specificity, the female to male ratio varies depending on the specific auto-immune disease [155]. Preliminary evidence seems to support this notion with respect to the conditions, showing time-based undulations arising out of the outbreaks [128]. One of the key features of Fig. 7 is the general trend upward in the proportion of female admissions. Male mortality has been declining faster than that for females and this implies a more rapid expansion in the number of elderly males, which is the opposite to the increasing proportion of female admissions, i.e. an additional factor is at play.

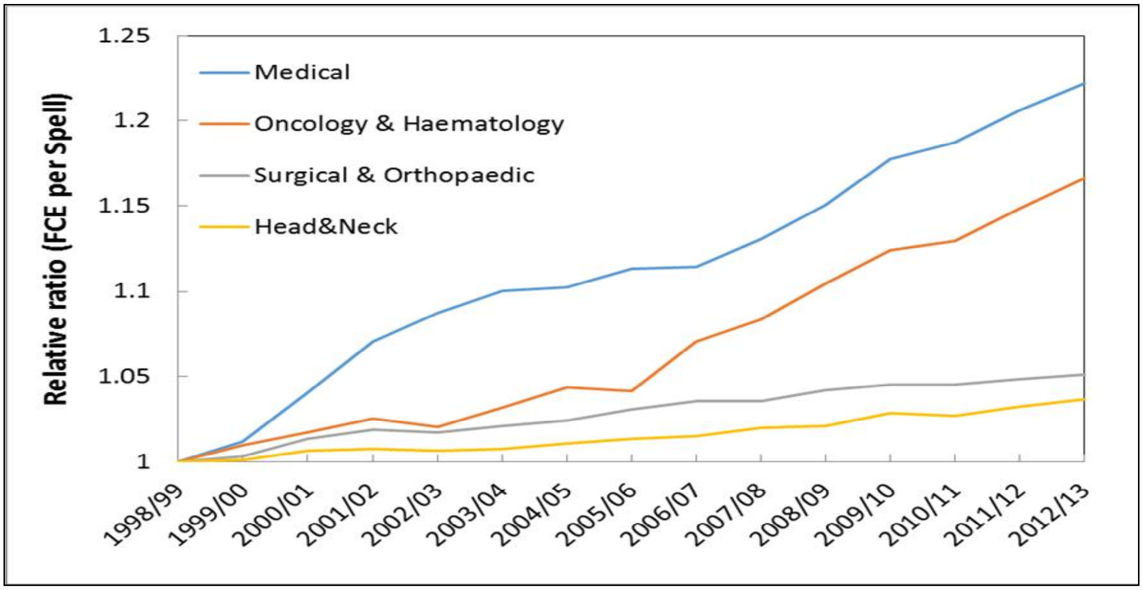

Fig. 6. Growth in FCE per Spell (overnight stay admissions)

Day case admissions excluded. 1998/99 is taken as the reference point and the FCE per Spell is relative to this point. The trend line tends to go flat just before an outbreak

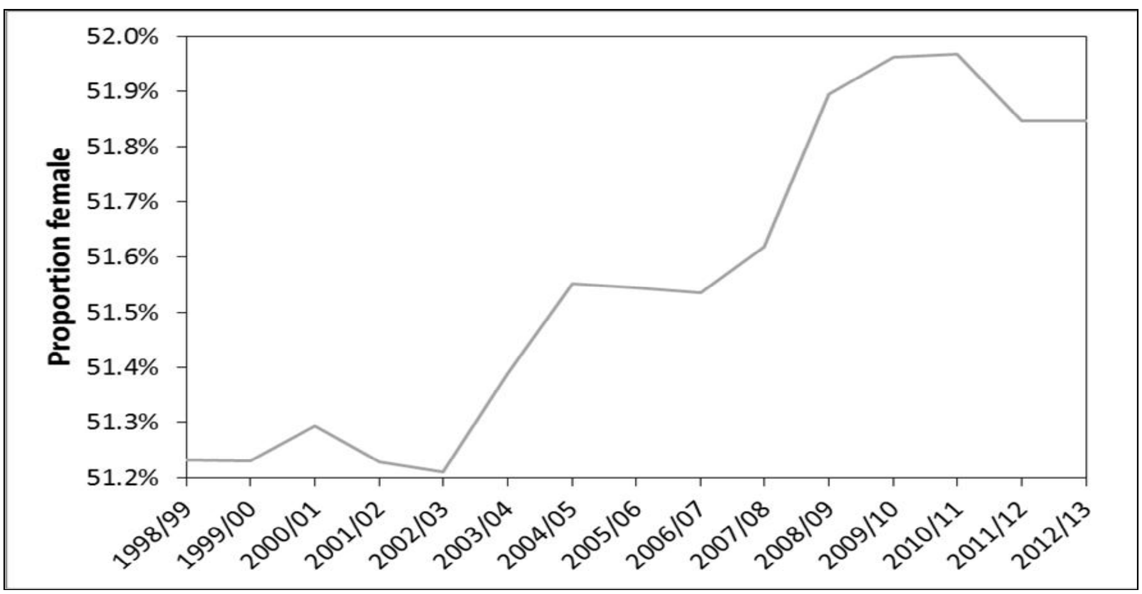

Fig. 7. Cycles in proportion female for medical group admissions

Data is for Finished Consultant Episodes (FCE), and includes all admission types. Note the cycle reaches a maximum several years after the start of the outbreaks. The small peak in 2000/01 reflects partial spread of the 1998 outbreak in England. The trend line tends to dip down or go flat just before an outbreak

5.4 Occupied Beds

The initiation of a bed crisis is commonly associated with these outbreaks [1,3,7,11,58,64,68,73,118,120]. The rise in occupied beds during these outbreaks is partly due to increased medical admissions and a direct link between bed utilization and end-of-life care [156]. This is illustrated in Fig. 8 (which has been length of stay adjusted). Recall that the picture presented in Fig. 8 is a composite arising out of spread across the UK over a two year period. At local level the shift to higher bed occupancy is far more step-like [57-58,129]. However, note the time-based undulation in occupied beds with initiation at the point of the infectious outbreaks. Such increased bed occupancy then places considerable pressure on waiting times in the emergency department (ED). The ED is already under pressure due to the increase in attendances associated with the outbreak, and the associated shift to a more complex case-mix [26,29,33,45-49] and bed non-availability only makes these pressures worse [134-135,139]. Hence the whole issue of operational resilience and bed numbers has been made more complex by the unacknowledged presence of these infectious outbreaks.

5.5 GP Referral to Outpatients

The increased GP referral which accompanies these outbreaks is a clear sign that this is not some acute hospital threshold issue. There are time-lags between referral to different specialties [51] and time lags between regions [50]. Within Dermatology there appear to be further long-term condition-specific time cascades [52]. Referral to particular immune-sensitive specialties has been shown to increase after the 2012 outbreak in England [54]. The key observation is that GP referrals appear to be very sensitive to the particular strain behind each outbreak.

5.6 Role of Sunlight/Vitamin D

A key finding of the more recent studies is a potential role for Vitamin D. There has been an explosion in the research indicating the profound importance of vitamin D in immune modulation and hence human health and death [157]. Vitamin D levels lag by around three months after peak sunlight levels, and the transmission of the infectious agent reaches a definite minimum in August, the point at which Vitamin D levels reach a maximum [59].

The potential role for Vitamin D sufficiency/summer appears to explain the general north to south movement of each outbreak and offers a possible explanation for the apparent failure of the 1999 (and several earlier) outbreak(s) to spread across large parts of England. See Section 6 for further discussion in the context of spread across Europe.

5.7 Interaction with Influenza

It has been observed that a decline in influenza activity to a 100 year minimum in early 2000 greatly facilitated unambiguous demonstration of these outbreaks [7]. Interestingly it has been proposed that an outbreak earlier in a year may act to potentiate the effect of the usual winter or seasonal influenza infections [19,57]. A re-appraisal of the role of these outbreaks in former influenza epidemics is warranted. A time series for these outbreaks going back to the early 1950's has been given elsewhere to aid such endeavors [38].

5.8 Increased Costs

Each outbreak is accompanied by a cycle of financial surplus and deficit, which has been evident in the NHS in the UK and in the health insurance industry in the USA over many years [7,38,42,140-141]. In England, the author has observed that around the time of the outbreaks particular PCO's suddenly seem to experience financial 'failure' for which there is no adequate explanation other than the fact that emergency medical admissions had increased, for no apparent reason [57,114,124]. This has been interpreted as evidence for 'incompetence' and 'failure' to manage demand, hence, the current governments belief that privatization will introduce more cost effective management. However the alternative explanation is that the agent appears to spread across the UK over a two year period, and hence, there arises a confusing jumble of hospitals and PCO's which are, and are not affected in particular years [37-38,57,80].

Since each outbreak leads to a large increase in elderly deaths, who may have otherwise gone on to consume health care resources, some could argue that the outbreaks are in fact cost saving. However, it should be pointed out that each outbreak appears to generate 10-times more medical admissions than deaths and appears to result in a cumulative increase in admissions [7,20,31,41,44], i.e. unlike an influenza epidemic these outbreaks appear to leave a cumulative legacy. Hence the rapid expansion in medical share in Figs. 1 and 5. For particular conditions, this cumulative legacy results in a stair case like increase over time, with the major part of growth occurring at the step-up part of the stair case shaped trend [31,41,44].

Should the agent prove to be CMV, then the bulk of research points to a significant potential reduction in the prevalence and/or severity of symptoms for certain neurodegenerative, digestive system, respiratory and cardio/vascular conditions [40,41,137]. It would seem that the effect of prevention may well be a net cost saving. Further research is urgently needed to clarify these issues.

6. EUROPEAN PERSPECTIVE

Evidence for the spread of this agent in Australia, Canada, UK and USA has already been presented. Fig. 9 presents data covering 27 European countries where the maximum step-like increase in deaths was calculated for each country for the period covering three outbreaks occurring around 2003, 2008 and 2012. For each outbreak the magnitude of the step-like increase was calculated using the highest value of the increase in deaths at the start of the outbreak, or the decrease at the end of the outbreak. Most of the 2003 outbreak estimates used the decrease following the outbreak simply because insufficient data was available to fully characterize the increase at the start. The log-log relationship arises from the effect of size and the modifiable areal unit problem (as discussed earlier). Countries lying appreciably above the upper-trend line in Fig. 9 are Cyprus, Luxemburg, Italy and France. As can be seen from Fig. 9, spatial areas containing around 2,000 to 3,000 deaths can be used to derive a clearer picture of the spread within a country, although statistically significant results can be obtained for any areal unit with more than 300 deaths. See Supplementary material for more detail.

The generally lower percentage increase observed in Germany, is of interest since it appears to have lower CMV seroconversion rates [158-159], and a lower proportion of the population which is CMV seropositive [160]. Further research is required in this area. The low apparent value observed for Estonia, is partly due to an ongoing reduction of around 28 fewer deaths every month since 2002. Adjustment for this factor takes the size-adjusted percentage increase up to 7%, a figure almost the same as that for Germany.

Latitude and the log of population density appear to play a weak role in the percentage increase (See Figs. S1 and S2 in the supplementary material). Neither appears to play a strong role regarding apparent initiation date. To explore further countries were then ranked in order of initiation during each outbreak Fig. 10. As can be seen, the outbreaks tend to occur earlier in Denmark, Romania, Bulgaria and Slovakia, while they tend to occur later in UK, Belgium, Greece and Slovenia. Denmark and Slovenia showed the least variation in ranked order. Further research is required to see if this is a statistical artefact of only three outbreaks or if there are other explanatory factors.

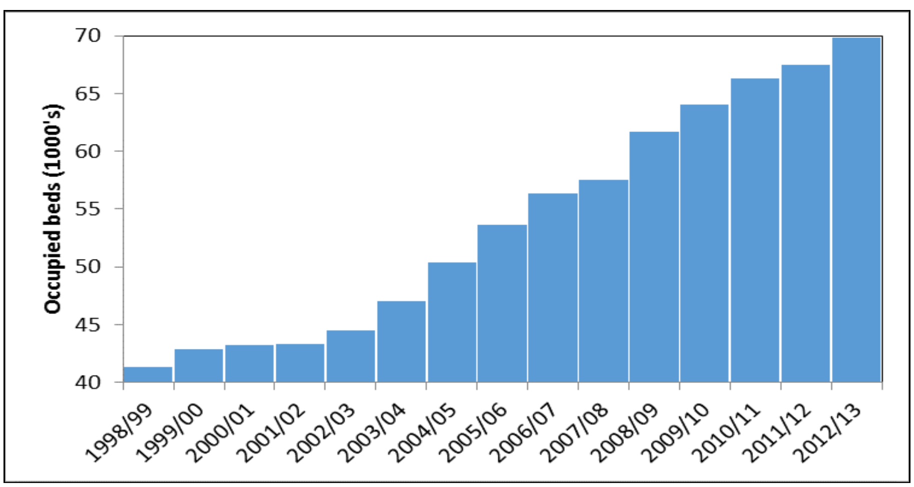

Fig. 8. Growth in occupied beds (LOS adjusted) for the medical group

Occupied beds adjusted to 2012/13 average length of stay (LOS). Note that the rate of increase declines just before an outbreak leading to the step-like increases in bed pressure in 1999/00, 2003/04, 2009/09 and 2012/13

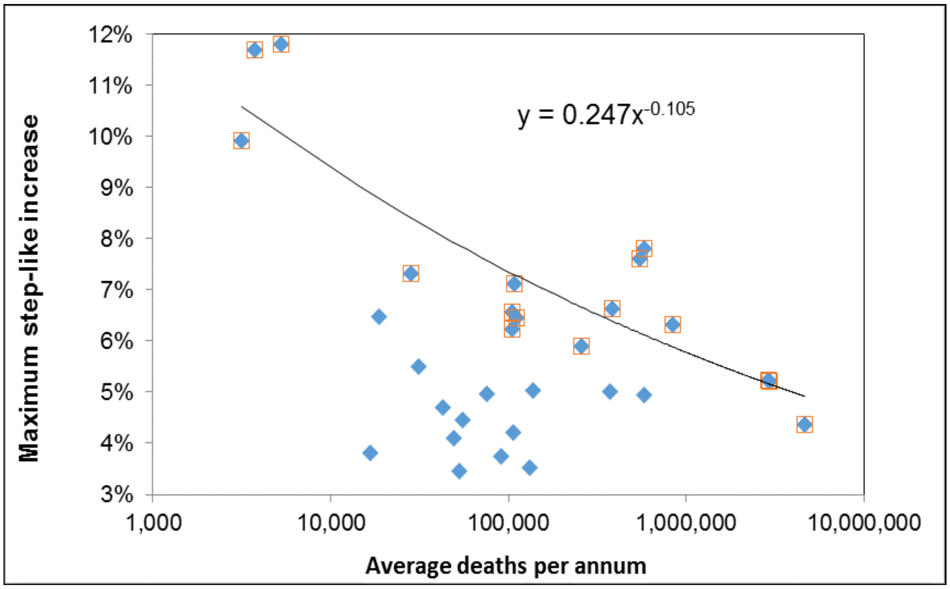

Fig. 9. Maximum step-like increase in deaths for 27 European countries between 2002 and 2013

Monthly deaths is from EuroStat and covers the period Jan-02 to Dec-13. Maximum step-like increase has been determined using a running 12 month total. Two larger EU areas are included and cover the earlier EU members (EU 16) and the extended EU area (EU27). The maximum step-like increase covers the 2003, 2008 and 2012 outbreaks. The trend line (Power law) covers the countries with the highest increase, outlined with a red square

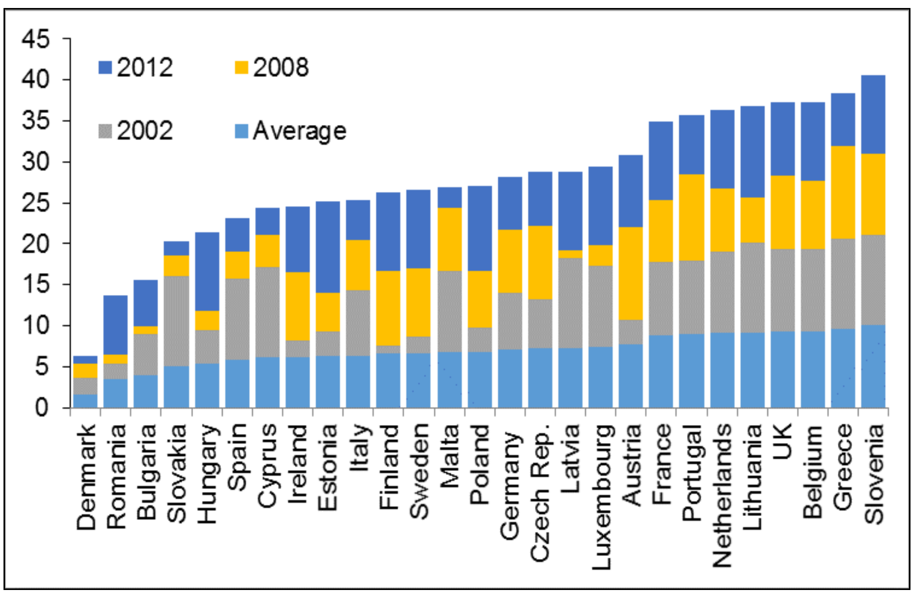

Fig. 10. Averaged ranked order for the three outbreaks

Order of each outbreak was ranked. All outbreaks were adjusted to a rank of 1 to 11. X-axis is the rank score. Maximum possible is 44, i.e. last country for the three outbreaks plus an average of 11

For example, the incidence of Kawasaki disease (KD) in England showed three peaks near to the 1993, 1996 and 1999 outbreaks [161]. An infectious origin has been implicated in KD [162]. In Japan, Hawaii and San Diego, KD cases appear to be linked to tropospheric wind patterns moving air from central Asia and traversing the north Pacific [162]. These and other possible associations will need to be explored to resolve these issues.

A month of year pattern for initiation has been observed in the UK with highest initiation in the winter months, especially those when vitamin D levels reach their minimum. Fig. 11 explores this association using the European data, and a peak in national-level initiation is seen in February and March. During the eight warmer months it is now generally agreed that latitude does not play a major role in Vitamin D levels since skin pigmentation, diet and efficiency of conversion tend to compensate for declining sunlight at more northern latitude [163]. However in the four cooler months latitude does play a role [163]. However a general degree of vitamin D insufficiency prevails across much of Europe [164]. The key issue is more likely to be the vitamin D status of these who are susceptible to infection and hence consequent hospital admission and death. The alternative is that the generally higher prevalence of winter respiratory infections in Jan/Feb [165] is acting to facilitate a respiratory mode of transmission. Figure S3 in the supplementary material gives further detail.

In the UK, the 2008 outbreak had a generally lower impact on deaths and admissions and Fig. 12 confirms that this was the case across Europe. Average increase across Europe was around the lower quartile seen in the 2002/2003 outbreak. Variable effects due to different strains of the same agent are implied. Recall that in the UK the 2012 outbreak stretched into 2013, but at present there is insufficient European data (until the EuroStat data is updated), to establish if this occurred more widely.

After adjusting all 27 countries for the effect of size on the percentage increase (using the equation in Fig. 9), total deaths during these outbreaks could account for over 467,000 deaths. Due to the dampening effect of spatial spread on the apparent increase, this is probably a considerable underestimate. At a ratio of 10 extra admissions per death this implies that each outbreak adds a minimum of £9 billion into health care costs across the EU. A European-wide study is urgently required using small area data covering both medical admissions and deaths to establish the detail around the spread across Europe.

We are clearly dealing with an international phenomena of profound public health importance with potential for over one million deaths around the world during each outbreak.

7. CONSEQUENCES OF THE DISCOVERY

7.1 Medical Research

The ability of immune function to influence over 100 inflammatory conditions and over 100 auto-immune conditions, is a salutary testament to the vast opportunities for an immune modulating agent to influence the rate of development and severity of multiple diseases [7,42,143-144]. The search for this agent needs to be accelerated as does an understanding of how such wide ranging effects are achieved.

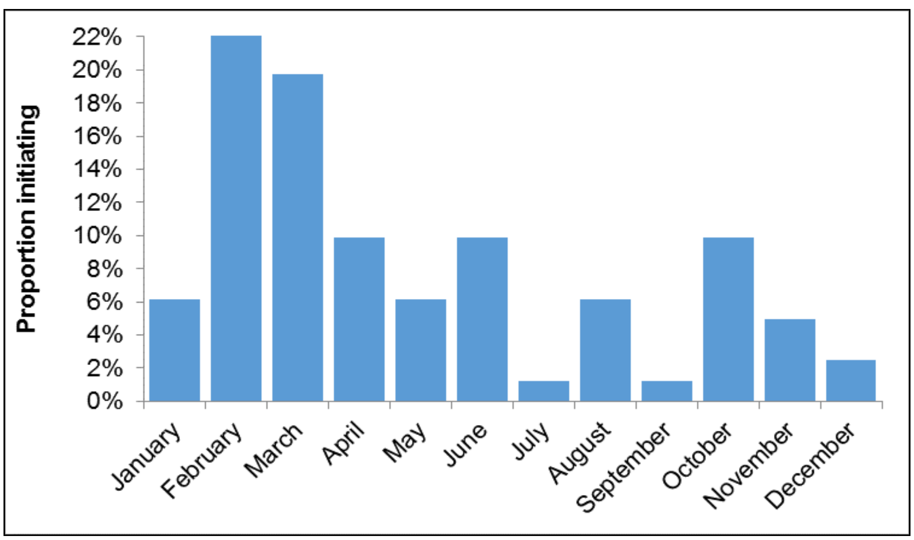

Fig. 11. Month of apparent initiation in 27 European countries across three outbreaks

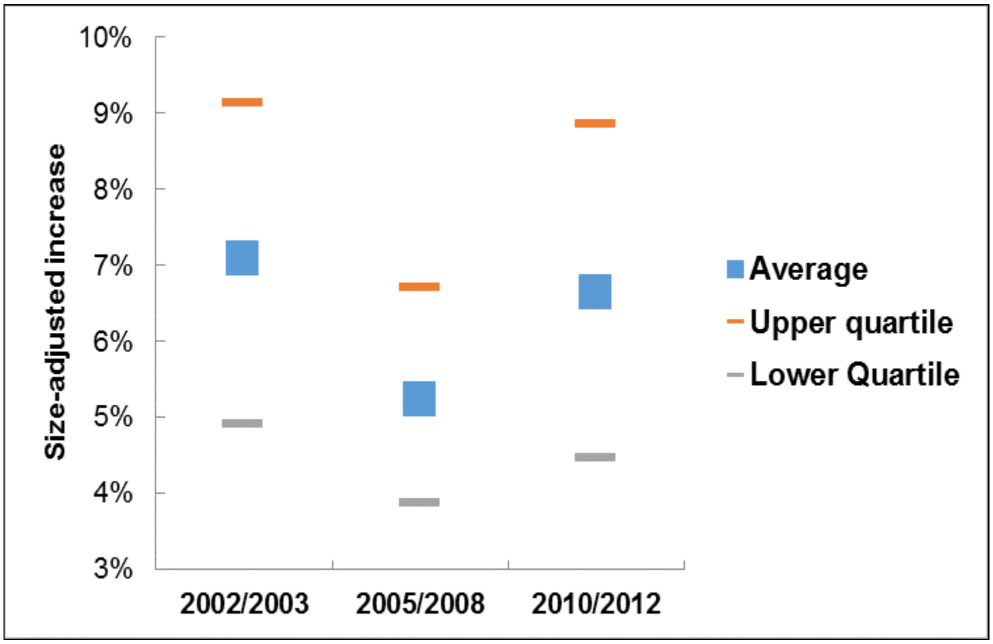

Fig. 12. Magnitude of the step-increase in deaths for the three outbreaks in Europe

7.2 Health Care Policy

The success of policy relies upon elucidation of cause and effect. Recent policy by the government of England to introduce privatization as a solution to the problem, is partly based on an absence of the realization of the profound operational and financial consequences of these outbreaks. Perceived financial failure is the result of what appears to be an unacknowledged infectious outbreak, and this cannot be resolved except through appropriate public health measures.

7.3 Cost Volatility

There are over 1,400 species (540 bacteria, 320 fungi, 210 viruses, etc) infecting humans of which 58% are zoonotic [166]. One to two new viruses alone are discovered each year [167], and a single study in Utah (USA) discovered 673 novel/new bacterial species (110 novel genera and 95 novel taxa) in clinical samples [168]. Hence these infectious outbreaks are occurring against a backdrop of multiple national and local outbreaks many of which will be unrecognized. A study of emergency admissions to gynecology, urology and general surgery over a 15 year period concluded that the knock-on effect of infectious outbreaks, via their ability to exacerbate general symptoms for other conditions, are probably playing a far greater role than is widely appreciated [106]. Hence the observation that cost volatility in health care is already very high [169-172] and is only made worse by these outbreaks [173-174].

Based on the effects upon case mix, bed days and PCO programme budget costs, it has been estimated that each outbreak adds around £600 million of costs into the NHS in England [124,170]. This is probably a conservative underestimate as the effects against primary care (GP visits, drug costs, community nursing, etc) and social care have not yet been evaluated. As expected, admissions (and hence costs) are most volatile for the medical group of specialties and for mental health conditions [49,142]. The immune-sensitivity of a variety of mental health and medical conditions appears to be the common link [175-176]. The link with deaths creates high volatility in end-of-life costs [171].

7.4 Capacity & Financial Planning

The very fact that medical admissions are reflecting a fundamental infectious spread has obvious implications to capacity planning and maintaining operational resilience. The need to maintain correct levels of hospital occupancy, which for most hospitals is well below the 85% figure wrongly assumed to apply in healthcare, becomes even more important [177-182]. These outbreaks also appear to increase the day-to-day volatility in medical bed demand making capacity planning even more challenging [183].

The consequences of these outbreaks upon total health care costs in the USA have already been illustrated elsewhere [7,42,115]. Similar cycles of surplus and deficit have been observed in the UK [115,140-141,170] and can be partly ameliorated or exacerbated by the relative funding. For example the 2003 outbreak and the ensuing spread occurred during a period of rapid expansion in NHS funding [184], and this expansion in funding acted to dilute the financial impact. The fact that the outbreak can arrive in a particular location at almost any time in a financial year [24,43-45], leads to a high level of uncertainty in forecasting year-end activity and costs [173-174] which can be interpreted as a ‘lack of competence’ rather than a genuine issue arising from inability to know the future, and in particular the highly variable timing and extent of impact of each outbreak [24,43-45].

7.5 Funding Formula

The funding formula employed by the NHS in England (and other countries) relies on the assumption that health care costs arise from demographic and personal health-related issues [106]. A highly granular infectious outbreak showing slow spatial spread is the Achilles heel in attempts to prime these formula [114]. Hence, a more sophisticated approach is required for funding for those conditions which are affected, as opposed to those which are not. In the latter case the traditional formula approaches remain reasonably valid.

7.6 HRG Tariff

The Health Resource Group (HRG) tariff, which is similar to the DRG tariff employed in other countries, relies on the assumption of ‘steady state’ in cost behavior for both fixed and variable costs [114]. In England, the tariff is implemented based on costs collected three years earlier. Given that the cycle time is most commonly around five to six years, this implies that costs are collected in a trough and implemented in a peak – an effect which only acts to amplify financial instability.

Far more attention needs to be paid to the consequences of these cycles on the costs of these diagnoses/conditions which are effected by the outbreaks, and Fig. 6 relating to the effects of the outbreak on FCE per Spell complexity is apposite.

7.7 Age-adjustment

The role of single-year-of-age specificity is very important. In Berkshire an attempt to use traditional five year age bands failed to predict the effect of the 2012 outbreak at small area level. It was only when single year adjustment was applied could the effect at small area level be approximated [59]. Attempts to age-adjust medical admission rates, the calculation of hospital standardized mortality rates (HSMR) and studies looking at admission rate differences between GP practices are likely to be influenced by this effect.

Indeed careful scrutiny of studies attempting to explain variation in practice medical admission rates show that most studies collect data straddling an outbreak or near to an outbreak and use a variety of age-bands to standardize the data. Hence there is an unrecognized source of year-to-year bias [5,185-189].

For example, a study of medical admissions across Glasgow (Scotland) during 1997 noted a 4-fold variation in admission rates between GP practices even after adjustment for age (10 year age bands), gender and deprivation score [190]. This study occurred immediately after the 1996 outbreak which initiated in Scottish Local Authority areas between Mar-95 and Feb-97 and around Jan-96 for Glasgow as a whole [56]. Recall that there is far greater granularity regarding start date and percentage increase when measured at the level of individual GP practices [57], and that the increase endures for a minimum of 12 months. Hence to what extent is the observed 4-fold difference in admission rates to do with the use of 10 year age bands rather than single-year-of-age adjustment, or to the known high spatial granularity known to be associated with these outbreaks?

Likewise, two studies on avoidable admissions to 129 English hospitals and 150 PCOs used data collected from 2008 to 2011 [188-189]. A major outbreak occurred in the UK in 2007/2008. Once again, to what extent did age standardization (which only used 7 broad age bands (0-4, 5-14, 15-44, 45-64, 65-74, 75-84, 85+) and granularity in timing and extent of the effect of the outbreak contribute to the 15% of unaccounted variation in admission rates?

7.8 Balance between Acute and Community Care

Around the world health care systems are seeking to shift care out of an acute setting into community settings, and especially so regarding end-of-life care. The existence of an infectious phenomena showing highly granular small area spread presents considerable challenges to capacity planning for community-based services [114]. Existing studies have demonstrated anywhere between a 10% to a 100% (most commonly 30% to 40%) increase in medical admissions at small-area level, i.e. around 7,000 population [57-59], and the corresponding health and social care systems will experience corresponding step-changes in demand and be consequently over-run, leading to acute admission as a default.

8. BARRIERS TO ACCEPTANCE

8.1 Established Theories

Having presented the evidence it is apposite to consider why it has taken so long for this outbreak to be recognized. My own 22 year career in the NHS suggests that a large part of the explanation as to why, revolves around the cluster of outbreaks in 1993, 1996 and 1999 which had a profound impact on apparent growth in medical emergency admissions. This huge growth did not go unnoticed and a range of national and international studies attempted to understand what was happening. These studies have been discussed in Section 2.2.

In the absence of the consideration that this may be an infectious event, all studies sought to explain what was happening from a health and social care context. From a political perspective the policy makers seized upon these studies as:

1. Evidence that the process of health and social care were ‘broken’ and needed ’fixing’, and
2. Because the ‘problem’ lay in process of care this was then, surely, highly amenable to government health and social care policy

Such thinking became so entrenched that no one was able to think outside of the box and anyone who attempted to do so was shouted down by the majority. Indeed I was largely forced to publish what was effectively a wide ranging epidemiological study in a management journal simply because approaches to medical journals were rejected with a polite ‘we do not publish hypotheses’. It would seem that the conclusions were seen to conflict with what everybody ‘knew’ was true, and if a huge infectious outbreak existed it would surely have already been discovered.

Being forced to publish in a management journal, has in my opinion, had many advantages. Research which would normally be confined to the sphere of more academic medical journals had to be earthed in the day-to-day reality of health care capacity and financial planning. Up to this point the public health function had failed to translate the principles of epidemiology into their every-day implications to capacity and financial planning and risk. As a result no one understood why health care costs were behaving in the way they did. The finance professionals and economists had also missed the significance of the health insurance underwriting cycle in the USA, and had attempted to interpret it from a purely financial/economic perspective. Hence publishing via this route forced me to package the epidemiological/medical concepts in a way that would be understood by management and would explain why costs and capacity/operational management was so seemingly difficult. In the absence of this explanation, policy has been partly based on flawed ‘hidden assumptions’ regarding how health care is supposed to behave.

Obviously there are clear deficiencies in aspects of health and social care and their associated processes. There always have been, and always will be – health care is simply too complex to achieve perfection. However this widely perceived ‘truth’ about wider efficiency prevented people from seeing the bigger picture and being able to disentangle cause and effect.

8.2 Disruptive ‘Technology’

Disruptive technology is a term coined by Harvard Business School professor Clayton M. Christensen to describe a new technology that unexpectedly displaces an established one. His book, "The Innovator's Dilemma," separates new technology into two categories: sustaining and disruptive [191]. Sustaining technology relies on incremental improvements to established technology. Disruptive technology lacks refinement, often has performance problems because it is new, appeals to a limited audience, and may not yet have a proven practical application. For example, Alexander Graham Bell's "electrical speech machine", now the telephone.

Of relevance to health care is the fact that large corporations, i.e. Department of Health, are designed to work with sustaining technology. They excel at knowing their market, staying close to their customers, and having a mechanism in place to develop existing technology. Conversely, they have trouble capitalizing on the potential efficiencies, cost-savings, or new marketing opportunities created by low-margin disruptive technologies. Christensen demonstrates how it is not unusual for a big corporation to dismiss the value of a disruptive technology because it does not reinforce current company goals (policies), only to be blindsided as the technology matures, gains a larger audience and market share and threatens the status quo. The discovery of the role of Helicobacter pylori in the development of stomach ulcers is a medical example of a disruptive technology. On that occasion, the discoverer had to drink a culture of the bacterium before the status quo was finally altered [192].

The infectious outbreaks introduced the conceptual equivalent to 'disruptive technology' into our understanding of how health care demand behaves through time. The existing incremental technology (demographic-based growth), has been demonstrated to fail in the real world, and unheard of 'disruptive' concepts such as 'cycles', 'step-like changes', and 'spatiotemporal spread' have been proposed to offer better insight into how costs behave over time. The combined and interactive effects of the environment (weather, air quality, infectious outbreaks), have been proposed as a major contributing factor in these disruptive changes and explain why it is almost impossible to run a balanced health care budget. Hence changing commissioners from Primary Care Trusts (PCTs) to Clinical Commissioning Groups (CCGs) in the Lansley health 'reforms' of the NHS in England, was mere window dressing based on the old incremental 'technology' and its hidden assumptions.

It would seem that we need to have a fundamental re-think around how we forecast future. Health care activity and costs, i.e. the new 'technology', which utilizes different concepts to explain how health care demand behaves and mathematical tools rather than machines. The fundamental forces leading to such large magnitude changes need to be far better understood, since if this is not achieved then CCGs will be subject to the same cycle of surplus and deficit as were the PCTs before them. Can the Department of Health rise to the 'disruptive technology' challenge or will they, like large corporations, dismiss the opportunity because it conflicts with accepted wisdom and cherished policies?

8.3 "Policy Based Evidence"

The issues elucidated in this review present a moral and ethical dilemma to Health Departments in the Western world. Indeed much health policy seems predicated upon the assumption that growth in excess of that predicted from demographic trends is 'abnormal' and is evidence for broken and /or inefficient health services which require 'fixing'.

Several examples are probably apposite. First, in early 2013 the media became aware that deaths had mysteriously increased in England and Wales, and several newspaper articles discussed potential causes. In the midst of mounting interest and speculation, Public Health England published a letter in which it was stated "After reviewing the analyst's circulated report within PHE, it was clear that there were potential methodological weaknesses with the approach" [see 193], and published a report investigating deaths during the winter of 2012/13 in which it was implied (but not stated) that the deaths were probably due to a bad winter. This report omitted to mention the key fact, that the deaths had increase in early 2012 and were still high after the winter of 2012/13 had ceased [236. Indeed the assertion of 'potential methodological weaknesses' could probably be disputed [36]. However, the consequence of this letter and report was to divert media, and open public scrutiny away from what now appears to be a major infectious outbreak, and allowed notions that the problem was to do with inefficient health services to continue to go unchallenged.

The second example comes from a letter by Professor David Oliver (a former national clinical director for older people at the Department of Health) which was published in the British Medical Journal. He discusses how the Department of Health was obsessed with a 'quick fix' mentality in which the evidence was chosen to support policy, i.e. "policy based evidence" rather than the development of evidence based policy [194]. In a remarkable coincidence, several months later experienced political commentator John Seddon published a book 'The Whitehall Effect' examining how the deleterious effects of the wider effects of "policy based evidence" can be discerned across all manner of public services [195].

No one would ever deny that both continuous and breakthrough improvement(s) have been, and will always be, required in health care and indeed any other aspect of government and industry. The issue is around correctly attributing cause and effect in a manner unimpeded by 'politics'.

The third example comes from the area of financial planning and risk. Once again the hidden policy assumption has been that, since growth is driven by demography, therefore financial planning should be straight forward and financial risk should be minimal. Over the past 10 years this author has consistently pointed out that financial risk in health care commissioning (purchasing) is very high, and is made even worse by the existence of these outbreaks [119,122,127-128,140-142,171,183,196-209].

During the recent Lansley 'reforms' of the NHS, the Chairman of the Royal College of General Practitioners (Prof. Clare Gerada), repeated attempted to get the government to acknowledge these risks, and on no occasion has any of this extensive work ever been cited in Department of Health documents. It would seem the doctrine of "policy based evidence" simply chose to ignore any evidence contrary to policy. As a result, Primary Care Organisations (the commissioners of health care), have been left to flounder in uncertainty as to the real causes of the financial cost volatility and cost pressures which they have experienced in recent years.

Hence should government departments acknowledge the existence of these 'cycles' and the possibility that they are from an infectious source? To say nothing is to deny the existence of hard data demonstrating that something unique is happening in a recurring manner. Such a 'sin of omission' then perpetuates the false assumption that the trends are evidence for policy-centric interventions. Indeed it withholds from planners the key knowledge that many of the trends in admissions, GP referral, bed demand and costs may be cyclic and involve time-based disease cascades.

Likewise to deny a potential infectious source would be unwise given the weight of evidence suggesting such a possibility. To suggest that the public may become needlessly alarmed is to suggest that the public are incapable of understanding that these events have happened in the past and will continue to happen until medicine can find a solution. This is no different to many other (currently untreatable) diseases.

Whatever the chosen communication route it would be highly imprudent not to initiate further research.

9. CONCLUSION

It is hoped that this review has presented sufficient evidence to show that many years of evidence for an infectious outbreak has been ignored and misinterpreted. The underlying issues have been presented to enable researchers and policy makers to see that we have a serious public health issue – one which masks the current obsession with just process and cost. My research finding may go some way to explaining the apparent failure of policy and cost control initiatives.

The potential for effects on the marginal and time-based expression of a surprisingly large number of conditions/diseases is of profound medical importance.

It would seem clear that research needs urgently to switch to identifying the infectious agent, understanding the pathways of immune modulation and developing effective vaccines, or perhaps exploiting the pathways of immune modulation. The necessary research has been detailed in several publications [7,22,40-42].

CONSENT

Not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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