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A Study of an Unexplained and Large Increase in Respiratory Deaths in England and Wales: Is the Pattern of Diagnoses Consistent with the Potential Involvement of Cytomegalovirus?

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Author's contribution

Author RPJ was responsible for all design, analysis and wrote the paper.

Original Research Article

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ABSTRACT

Aims: To determine if the ubiquitous herpes virus, cytomegalovirus (CMV), could be involved in a large and unexplained increase in all-cause mortality in England and Wales in 2012, and more specifically if this involvement was via a respiratory etiology.
Study Design: Analysis of respiratory system cause of death in England and Wales and of respiratory system emergency hospital admissions in England.
Place and Duration of Study: Cause of death statistics with primary respiratory system involvement in England and Wales in 2011 and 2012. Trends in emergency hospital admissions in England where there is a respiratory system primary diagnosis over the period 2000/01 to 2012/13.
Methodology: Respiratory diagnoses which show a statistically significant increase as cause of death in 2012 were identified, as were diagnoses showing a statistically significant increase as the primary cause of an emergency hospital admission in 2012/13. These diagnoses were then compared with medical case studies for hospitalization and death due to CMV.
Results: Deaths in England and Wales showed a sudden and unexplained increase in early 2012 which continued for 18 months before abating. The increase was equivalent to a large influenza epidemic, although higher levels attributable to influenza were absent. The increase was age and gender specific, and highest among those with neurodegenerative diseases (+15%); however, due to the way in which the primary

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cause of death is coded the role of respiratory diseases as the trigger for decease can be obscured. The next highest increase was for respiratory conditions, the most notable for bronchiectasis (+19%), asthma (female +14%), lung diseases due to external agents (+12%), interstitial pulmonary diseases (female +12%), chronic pulmonary disease (+7%) and a range of other conditions with >4% increases. After adjusting for the way in which deaths in the dementia group are coded the increase due to pneumonia rises to +8% for males and +15% for females. For the whole of the respiratory group augmented with the dementia group the increase in deaths was specific to those aged over 65 (average for 65+ of male +8.3%, female + 8.7%) with a peak at 90-94 (male + 15%, female + 17%). A corresponding large increase in respiratory admissions accompanies the increase in deaths. Given that the increase in admissions and deaths moved across England and Wales in a time-based spread, indicative of an infectious agent, with spurts of rapid local spread compatible with respiratory transmission, the increase in respiratory deaths were examined to see if the nature of any putative infectious agent could be discerned. There was a striking match with the known clinical effects of CMV.

Conclusion: In an aged population lifelong exposure to the immune erosive effects of CMV presents the potential for the emergence of diseases reliant on immune impairment for their modus operandi. The lung is a primary reservoir for permanent CMV infection in humans and conditions/diagnoses showing a large increase in both death and hospital admissions in 2012 are all potentially CMV-mediated. In view of the very large increase in death for particular respiratory diagnoses further research is urgently required.

Keywords: Cause of death; ageing; respiratory conditions; immune impairment; cytomegalovirus; hospital admission; emerging infectious diseases.

1. INTRODUCTION

Due to ongoing improvements in life expectancy the number of deaths in England and Wales has been declining since the mid-1990's and is not expected to reach a minimum until around 2015 [1]. However around mid-2011 deaths in Scotland began to show an unexpected increase [2] to be followed by an equally unexpected increase in England and Wales in early 2012 [3] leading to a peak in deaths during the 2012 calendar year. In both instances the increase endured for around 18 months before abating. There were no unusual levels of influenza to explain the increase and the fact that the increased deaths endured for 18 months rules out typical winter respiratory viruses. This event also appears to be a repeat of similar events leading to unexplained peaks in deaths in the UK in 2003 and 2008 [4-5]. It seems likely that the presumed outbreak is due to a persistent infectious agent which is eventually bought under immune control and/or which kills susceptible members of the population leading to the eventual decline in deaths back to expected levels.

These infectious-like events are also associated with an even larger increase in medical hospital admissions and emergency department attendances which are age, gender and condition specific [6-9] and with a temporary wobble in the gender ratio at birth [10]. Small-area studies of the increase in medical admissions shows somewhat random spread over time of rapid increases in admissions which also endure for 12 to 18 months in each small-area before eventual decline [11-13]. Deaths associated with the 2003 and 2008 peaks also show evidence for spatiotemporal spread [4]. In Berkshire this spread appeared to affect predominantly Asian areas earlier than predominantly white British locations, although the increase in medical admissions was typically lower in the Asian areas [14]. When these small areas are aggregated up to Local Authority level the rise in medical admissions is

synchronous with the increase in deaths and has profound effects upon health care costs [6,9,12,15-17].

This study seeks to examine the increase in respiratory deaths during 2012 to see if there are patterns in the diagnoses which could give a clue to the nature of this presumed infectious agent.

2. MATERIALS AND METHODS

2.1 Data Sources

Total deaths by gender and single year of age from 1963 to 2012 in England and Wales was obtained from the Office for National Statistics (ONS). Cause of death statistics covering England and Wales were for the primary cause of death, coded by the ONS using the International Classification of Diseases (ICD) version 10 and from the ONS. Monthly births in England and Wales were obtained from the ONS. Hospital Episode Statistics (HES) admissions for respiratory conditions were obtained from the NHS Health and Social Care Information Centre website.

2.2 Adjustment for the World War II Baby Boom

The impact of contribution from the World War II (WW II) baby boom was determined for the 65-69 year age band (born 1943 to 1947). A 7.2% adjusting factor was determined for this five-year age band arising from the large increase in births within the space of a single year, namely a 28% increase in births in the twelve months ending March 1947 compared to the twelve months ending March 1946. Such an adjusting factor is not requited for the other age bands.

2.3 Determining Which Diagnoses Show an Increase

The observed sharp increase in deaths early in 2012 means that deaths in 2012 can be compared against 2011 to give a before and after comparison. Any diagnosis showing greater than a two standard deviation difference between the two years was investigated. Due to Poisson statistics, where the standard deviation (SD) is, by definition, equal to the square root of the average, the value of the SD can be estimated as the square root of the number of deaths in 2011. A Poisson distribution becomes increasingly left skewed for smaller numbers and for this reason diagnoses with fewer than 100 deaths in 2012 were also excluded from the analysis. The percentage increase was also calculated for the resulting diagnoses showing a significant increase.

Given the far higher number of respiratory hospital admissions the Confidence Interval (CI) was calculated from a Poisson distribution with admissions in 2012 compared to the average of 2011 and 2012, i.e. the null hypothesis that any differences between 2011 and 2012 are simply the result of random forces.

3. RESULTS AND DISCUSSION

3.1 Respiratory Mortality

Age standardization has not been required in this study for two reasons. Firstly, due to increasing life expectancy total deaths are expected to decline in England and Wales through to 2015 and hence an increase is an unexpected event [1,3]. Secondly, the change in the population age structure between 2011 and 2012 is so small that it would not influence any conclusions. The only exception affects the group aged 65-69 in 2012 and an adjustment has been applied to correct for the effects of the WW II baby boom.

All diagnoses/conditions showing greater than a two standard deviation increase in 2012 versus 2011 are given in Table 1 along with the number of standard deviations difference between the two years and the percentage difference between 2012 and 2011. For J18, J44.1 and J45 the matching pair for the male/female split has been included (*in italics*) for the sake of comparison even though the difference was less than two standard deviations. The most notable increases are for bronchiectasis (+19%), asthma (female +14%), lung diseases due to external agents (+12%), interstitial pulmonary diseases (female +12%), chronic pulmonary disease (+7%) and a range of other conditions with typically greater than 4% increases.

Several conditions showed a greater than two standard deviation reduction, the most notable being influenza which was typically -10% (data not shown). This observation tends to exclude influenza as a hidden explanation for the above diagnoses/conditions. While two standard deviations has been used as a nominal cut-off to exclude an increase arising from chance it is clearly evident from Table 1 that the majority of diagnoses/condition groups show greater than a three standard deviation difference which is an approximation for the 99.9% confidence interval, i.e. the increase is due to a factor other than random variation.

The apparent low increase for pneumonia is most probably due to the fact that around 50% of deaths coded to dementia, Alzheimer's and Parkinson's (hereafter called the dementia group) have pneumonia as the precipitating rather than primary cause of death [18-19]. Such an adjustment has been included in Table 1 (see [20]) where it can be seen that if 50% of deaths in 2011 and 2012 are assumed to be due to pneumonia in the dementia group then pneumonia *per se* becomes a highly significant cause of death. Unfortunately this is a crude adjustment and there may be some overspill into death from asthma and chronic obstructive pulmonary disease (COPD), etc. The calculated increase in Table 1 for non-pneumonia conditions can therefore be considered as a lower limit. The inclusion of the dementia group in the pneumonia deaths appears to be fully justified given the 15% increase in pneumonia admissions noted in Table 3 (see later for discussion).

Also worthy of note is that the major groups identified in Table 1 account for over 98% of all respiratory deaths. Based upon this observation the change in deaths between 2011 and 2012 using five year age bands was calculated for the entire respiratory group (primary cause of death ICD-10 J00-J99) with the addition of 50% of deaths in the dementia group and this is presented in Fig. 1. Use of this larger group (67,000 total deaths or 80,000 total deaths including a 50% share of dementia group) means that the five year age bands typically contain between 2,000 and 12,000 deaths for each gender and Poisson randomness is no longer a major issue in the percentage differences, and for this reason confidence intervals have not been displayed. Age group 65-69 has been adjusted down by 7.2% (percentage points) for each gender due to the large spike in births following the end of WW II.

Table 1. Respiratory diseases showing a significant increase in death in 2012

ICD-10	Description	Sex	2011	2012	STDEV	Change
J12-J18	Pneumonia	M	10,824	11,022	1.9	1.8%
J12-J18	Pneumonia	F	14,872	15,033	1.3	1.1%
J12-J18	Pneumonia (adjusted for dementia, etc)	M	18,143	19,544	10.4	7.7%
J12-J18	Pneumonia (adjusted for dementia, etc)	F	26,727	30,858	25.3	15.5%
J18	Pneumonia, organism unspecified	M	10,707	10,904	1.9	1.8%
J18	Pneumonia, organism unspecified	F	14,772	14,965	1.6	1.3%
J18.9	Pneumonia, unspecified	M	5,026	5,226	2.8	4.0%
J18.9	Pneumonia, unspecified	F	6,220	6,561	4.3	5.5%
J40-J47	Chronic lower respiratory diseases	M	13,539	14,378	7.2	6.2%
J40-J47	Chronic lower respiratory diseases	F	13,209	14,155	8.2	7.2%
J40-J44	Bronchitis, emphysema and other COPD	M	12,704	13,463	6.7	6.0%
J40-J44	Bronchitis, emphysema and other COPD	F	11,823	12,543	6.6	6.1%
J44	Other chronic obstructive pulmonary disease	M	11,932	12,748	7.5	6.8%
J44	Other chronic obstructive pulmonary disease	F	11,335	12,100	7.2	6.7%
J44.0	COPD with acute lower respiratory infection	M	6,270	6,658	4.9	6.2%
J44.0	COPD with acute lower respiratory infection	F	5,516	5,787	3.6	4.9%
J44.1	Above with acute exacerbation	M	1,459	1,523	1.7	4.4%
J44.1	Above with acute exacerbation	F	1,511	1,660	3.8	9.9%
J44.9	COPD unspecified	M	4,089	4,490	6.3	9.8%
J44.9	COPD unspecified	F	4,235	4,588	5.4	8.3%
J45-J46	Asthma	M	341	327	-0.8	-4.1%
J45-J46	Asthma	F	700	799	3.7	14.1%
J45	Asthma	M	330	316	-0.8	-4.2%
J45	Asthma	F	684	783	3.8	14.5%
J47	Bronchiectasis	M	494	588	4.2	19.0%

Table 1 Continued…….

J47	Bronchiectasis	F	686	813	4.8	18.5%
J60-J70	Lung diseases due to external agents	M	1,818	2,040	5.2	12.2%
J60-J70	Lung diseases due to external agents	F	1,302	1,485	5.1	14.1%
J61	Pneumoconiosis due to asbestos	M	161	189	2.2	17.4%
J61	Pneumoconiosis due to asbestos	F	3	4	0.6	33.3%
J69	Pneumonitis due to solids/liquids	M	1,472	1,657	4.8	12.6%
J69	Pneumonitis due to solids/liquids	F	1,266	1,449	5.1	14.5%
J80-J84	Other respiratory diseases	M	2,777	2,883	2.0	3.8%
J80-J84	Other respiratory diseases	F	1,687	1,888	4.9	11.9%
J84	Other interstitial pulmonary diseases	M	2,701	2,827	2.4	4.7%
J84	Other interstitial pulmonary diseases	F	1,628	1,828	5.0	12.3%
J84.1	Interstitial diseases with fibrosis	M	2,330	2,382	1.1	2.2%
J84.1	Interstitial diseases with fibrosis	F	1,406	1,523	3.1	8.3%
J84.9	Interstitial pulmonary disease, unspecified	M	344	421	4.2	22.4%
J84.9	Interstitial pulmonary disease, unspecified	F	211	287	5.2	36.0%
J95-J99	Other diseases of the respiratory system	M	1,973	2,253	6.3	14.2%
J95-J99	Other diseases of the respiratory system	F	3,409	3,618	3.6	6.1%
J98	Other respiratory disorders	M	1,968	2,250	6.4	14.3%
J98	Other respiratory disorders	F	3,390	3,598	3.6	6.1%
	Major Groups (as above)	M	31,766	33,491	9.7	5.4%
	Major Groups (as above)	F	35,865	37,791	10.2	5.4%

STDEV = standard deviation difference between 2012 and 2011, COPD = chronic obstructive pulmonary disease

Fig. 1 clearly shows age dependence, ranging from age-dependent reductions below age 65 and increases above. In theory the 95+ age group should also be adjusted down to account for another smaller spike in births following WW I and this would only accentuate the gap relative to the 90-94 age group. There is also a possible age-dependent effect relating to the 75-79 age group which is specific to males. At this point it is important to mention that the inclusion of a 50% share of dementia group deaths did not change the shape of the age response in Fig. 1 but led to a slight increase in the percentage increase above age 65.

The concept of a specific increase in death above age 65 and 85 is explored in Fig. 2 where the impact of the 2012 event can be clearly seen. Note the increase in proportion deaths for 65+ up to 1995 (due to increasing life expectancy) while this proportion remains relatively unchanged from the point at which total deaths begins to decline in the mid 1990's. At the same time 85+ deaths expand over the entire period from just 17% in the early 1960's to nearly 50% by 2012 and with most rapid expansion from the 1980's onward – of great importance if lifetime exposure to CMV is seen as an immune erosive force and especially given the problems of accurate diagnosis in the elderly [6]. Similar events to the large increase in 2012 can be discerned in earlier years, although if the bulk of an outbreak commences in mid-year then the increase is seen across two calendar years, i.e. 2002 + 2003, etc. Prior to 2000 these events occur alongside a series of large influenza epidemics which also act to increase the proportion of age 65+ and 85+ deaths. A degree of age specificity can be discerned where these two groups show a greater or lesser response to particular historic events. As can be seen the 2009 'swine flu' epidemic which peaked in England and Wales in early 2010 had only a small effect upon elderly deaths.

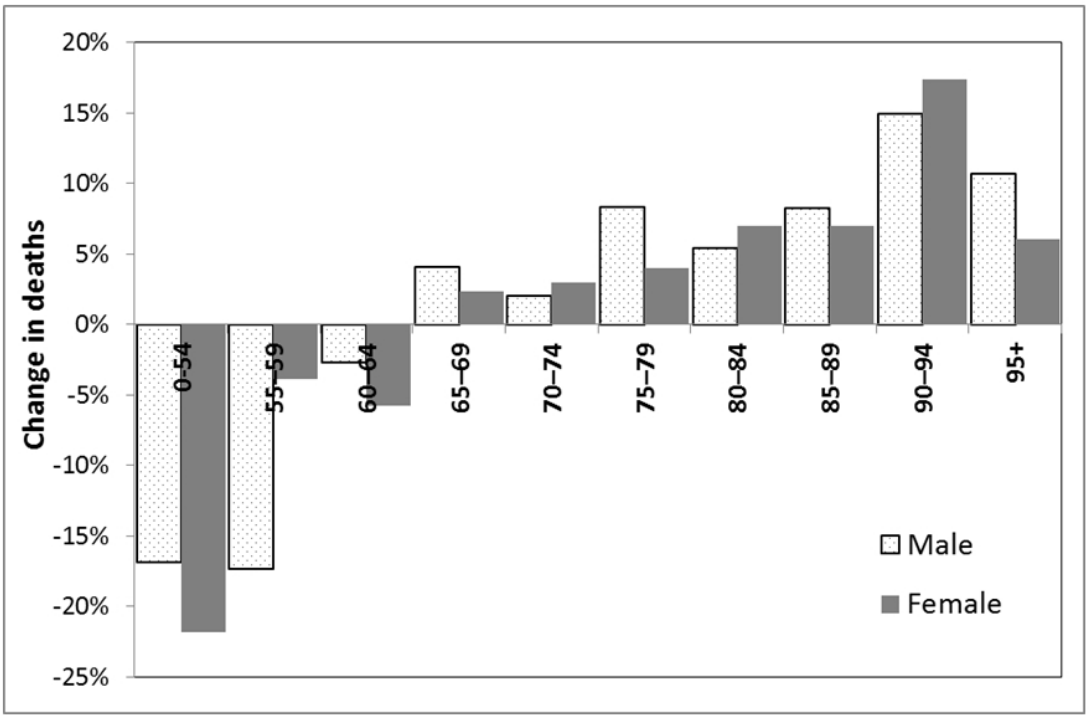

Fig. 1. Change in respiratory deaths (plus share of dementia group) in 2012 versus 2011

Table 2. Adjusted relative risk for cytomegalovirus infections (adapted from Miggins et al. [63])

Outcome	Bacteria alone	CMV alone	CMV and bacteria
Acute respiratory distress syndrome	1.8	5.3	4.2
Diarrhea	2.6	9.8	6.0
Pneumonia	2.8	4.7	4.3
Respiratory failure	2.9	3.6	4.1
Death	4.1	4.2	6.7
Multisystem organ failure	5.1	4.8	10.1
Sepsis	49	n/a	68
Septic shock	176	n/a	219

3.2 Increased Hospital Admissions

The increase seen in 2012 is part of a longer time series of these unexpected increases with deaths also peaking in 2003 and 2008 [1-6]. Data covering emergency admission to hospital in England (2000/01 to 2012/13) for respiratory conditions showing a statistically significant increase in 2012 are shown in Table 3. Fig. 3 presents the trend over time for total admissions showing a positive response to these outbreaks and illustrates the characteristic step-like increases in emergency admissions which are associated with the increase in deaths. The shape of the time trend in Fig. 3 is determined by spread of the agent within England [4,11-13]. This spread takes around two years but is facilitated by rapid 'outbreaks' at small area level, i.e. the implied respiratory phase of the infection, followed by 12 to 18 months of increased medical admissions. In theory, the trend line would probably start to fall if there was an extended period before the next outbreak. While there is good overlap between Table 1 and Table 3 in terms of diagnoses showing an increase during these outbreaks, it is important to realize that Table 3 will also contain non-life threatening respiratory admissions. It is also important to realize that only around 50% of deaths occur in hospital and when a person dies in hospital that the diagnosis reported as the cause of death may be different to that for the hospital admission. This is due to additional information which may be revealed during the post mortem and special rules applying to the coding of the primary cause of death [20]. However, from the 'all of the above' line it is apparent that a large 13% step-like increase occurred; which was a repeat of the events surrounding the 2003 and 2008 peaks in death and admissions.

This is not the first occasion where a respiratory link with these spikes in death and admissions has been observed, although the significance of the spike has not previously had a context for its interpretation. A study of deaths due to bronchiectasis in England and Wales from 1999 to 2007 clearly shows an age standardized increase in 2003 which extended into 2004 for those aged 75+, and especially for males [21]. Another study on pneumonia admissions in England between the financial years 1997/98 and 2004/05 shows evidence for peaks in admission, especially for those aged 85+ in 1998/99 and 1999/00 and again in 2003/04 and 2004/05 [22]. Once again these correspond with known dates for these presumed infectious events and especially for increases in medical admissions [2,6,11]. Similar long-term cycles can be discerned for asthma in both the USA and the UK [23-24] and asthma (especially for females) is another respiratory diagnosis showing a large increase in deaths during the 2012 event Table 1. Viral infection is the most common trigger for asthma in both children and adults [25].

Table 3. Emergency admissions for respiratory conditions showing an increase during 2012 in England

ICD	Description	2000/01	2002/03	2003/04	2007/08	2008/09	2011/12	2012/13	Change	CI
J00	Acute nasopharyngitis [common cold]	558	639	735	1,211	1,571	1,359	1,614	19%	100%
J02	Acute pharyngitis	3,058	3,183	3,546	4,462	4,453	4,502	4,794	6%	98%
J03	Acute tonsillitis	17,751	18,628	19,533	26,649	27,792	32,969	36,961	12%	100%
J04	Acute laryngitis and tracheitis	655	529	601	684	657	616	867	41%	100%
J06	Acute upper respiratory infections multiple	41,926	39,552	44,762	44,315	49,582	42,598	47,424	11%	100%
J10	Influenza due to identified influenza virus	106	97	283	112	275	698	1,389	99%	100%
J11	Influenza virus not identified	854	614	896	484	633	496	817	65%	100%
J12	Viral pneumonia not elsewhere classified	445	468	447	563	646	791	954	21%	100%
J14	Pneumonia due to Haemophilus influenzae	297	358	363	450	570	666	718	8%	84%
J18	Pneumonia organism unspecified	63,370	76,905	83,997	105,055	121,472	152,205	175,681	15%	100%
J20	Acute bronchitis	1,648	1,725	1,932	1,670	1,758	1,820	2,565	41%	100%
J21	Acute bronchiolitis	21,954	19,158	20,242	24,340	26,563	29,593	33,664	14%	100%
J22	Unspecified acute lower respiratory infection	65,165	68,503	74,861	77,632	88,032	83,327	98,138	18%	100%
J32	Chronic sinusitis	742	707	766	1,166	1,343	1,676	2,036	21%	100%
J36	Peritonsillar abscess	5,892	5,775	5,870	6,543	6,949	6,200	7,170	16%	100%
J40	Bronchitis not specified	1,155	1,047	1,198	1,462	1,621	1,750	1,880	7%	94%
J44	Other chronic obstructive pulmonary disease	84,721	87,942	99,590	96,602	106,561	105,101	113,301	8%	100%
J45	Asthma	50,687	49,409	54,378	53,916	59,525	50,451	57,312	14%	100%
J46	Status asthmaticus	7,902	7,232	6,753	6,724	7,339	4,808	5,528	15%	100%
J47	Bronchiectasis	2,816	3,212	3,697	4,291	4,643	5,886	6,821	16%	100%
J60	Coalworker's pneumoconiosis	29	27	24	16	14	14	22	57%	86%
J69	Pneumonitis due to solids and liquids	2,880	4,330	5,475	8,211	8,732	11,536	13,704	19%	100%
J70	Respiratory conditions due to other agents	61	79	73	105	110	113	148	31%	94%
J82	Pulmonary eosinophilia not classified	42	38	50	62	72	102	128	25%	89%
J84	Other interstitial pulmonary diseases	2,914	3,181	3,575	3,962	4,224	4,516	4,792	6%	98%
J90	Pleural effusion not elsewhere classified	9,735	10,445	10,726	14,569	15,076	15,033	15,385	2%	92%
J93	Pneumothorax	5,083	5,224	5,242	6,221	6,403	6,244	6,432	3%	88%
J96	Respiratory failure not elsewhere classified	2,198	2,646	2,844	4,346	5,365	7,153	7,686	7%	100%
	All the above	394,644	411,653	452,459	495,823	551,981	572,223	647,931	13%	100%

Selected years have been shown. See Fig. 3 for full trend over all years. The unexplained peaks in respiratory and other deaths occur in 2003, 2008 and 2012

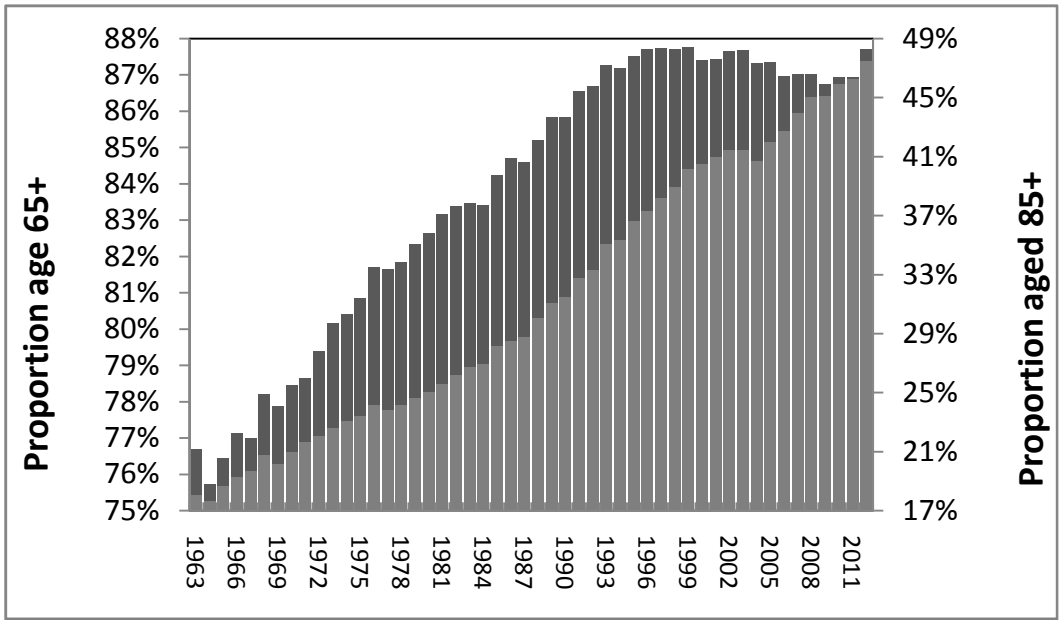

Fig. 2. Proportion of female deaths aged 65+ and 85+ by calendar year in England and Wales

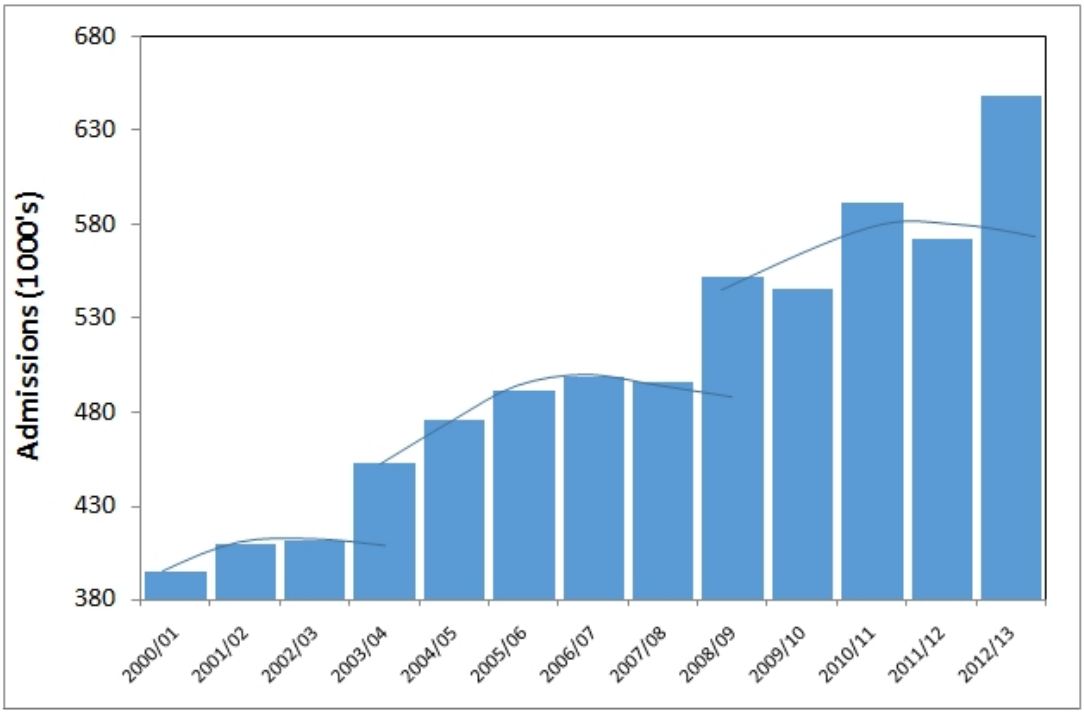

Fig. 3. Trend in total respiratory emergency admissions for diagnoses showing a significant increase in 2012

The validity of including the dementia group into the analysis of respiratory deaths is further supported by a study of geriatric rehabilitation patients where 31% had dementia and other neurological disease. Within three months after admission 39% had acquired a nosocomial infection with pneumonia and bronchitis being the most common [26]. Recent analysis of the deaths in England and Wales associated with the 2012 event has demonstrated single-year-of-age saw tooth patterns which are reminiscent of what is called 'original antigenic sin', the observed patterns in disease severity arising out of a series of infections with different strains of the same infectious agent [5]. These saw tooth patterns were first demonstrated for influenza [27]; however, deaths due to influenza in 2012 were far lower than in 2011 and this eliminates influenza as a causative agent. The same reasoning regarding influenza applies to the 2003 and 2008 peaks in death. Hence the agent we are searching for must have the capacity for population infection via a series of strains and an immune response is also involved. This rules out agents such as gonorrhea which do not elicit (or evade) an immune response [28].

The following discussion regarding the potential role for CMV should not in any way be interpreted as an attempt to argue that CMV is responsible for *all* lung disease (especially in the elderly), but rather an attempt to address the issue as to whether this widely prevalent virus could be implicated in the unexpected increase in deaths, i.e. in the marginal change.

3.3 Roles for CMV

It has recently been proposed that CMV may be associated with these outbreaks [6,11-12,16-17]. While the majority of textbooks/reviews suggest that CMV only poses a risk to the immune compromised, i.e. HIV/AIDS, transplant recipients, the fetus [29-34] and in primary immune deficiencies [35], the reality is that this virus is a vastly underestimated clinical risk factor in the supposedly immunocompetent population, especially for the elderly, where higher levels of CMV IgG antibodies are common (see later) as is active CMV infection [6,16-17,36]. CMV has profoundly powerful and wide-reaching effects against multiple aspects of adaptive and innate immunity [37-42] and physiology such as platelet adhesion and aggregation [43]. Indeed even during latent infection CMV is able to elicit immune-suppressive IL-10 producing CD4+ T cells [44], which starts to explain why CMV seropositivity alone can be associated with a host of deleterious health outcomes [45]. See next section.

Research into the immune modifying effects of CMV has grown rapidly since the early 1990's. A search in Google Scholar showed that 6,000 papers were published in 1993 mentioning CMV rising to over 20,000 published in 2010. The literature regarding the powerful immune modulating effects of CMV strongly support the notion that CMV should be a (largely hidden) risk factor in the elderly where a mix of what is called 'immunosenescence' and 'inflammageing' (especially in the presence of CMV) lead to a highly immune compromised state which is approaching immunosuppression [46-47]. For example, in allogeneic stem cell transplantation donor age was a significant risk factor in CMV-mediated post-transplant disease due to age-associated CMV differentiated T cells [48]. Such immunosenescence plus inflammageing aspects of ageing in the presence of vitamin D deficiency, which is common in the elderly, and especially in the institutionalized or house-bound [49-50] provides an additional and possibly synergistic layer of immune function impairment. Vitamin D (now recognized as a hormone) insufficiency is implicated in inflammatory lung diseases [51], leads to enhanced levels of hospital admission especially for respiratory conditions [52-53] and poor clinic outcomes [54-55]. The link between CMV and Vitamin D is made more clear given the known role of vitamin D receptor (VDR) gene

variants and CMV-mediated disease in transplant recipients [56-57] and the known roles for vitamin D in immune regulation [50,58-59]. Vitamin D levels are also known to be associated with levels of CMV antibodies (but not to other viruses) in pediatric-onset multiple sclerosis [60]. It would appear that ageing western populations where over 50% of medical admissions and 87% of female deaths Fig. 2 are for those aged 65+ are ripe for the hidden effects of CMV via a cumulative/synergistic set of immune impairments.

Systematic reviews of hospital case reports indicate severe life-threatening complications of CMV infection in the supposedly immunocompetent patient with a fatal outcome increasingly common above age 55 [61-63], see discussion later. Another recent review identified an increasing trend in CMV-related hospital case reports including wider involvement in inflammation and auto-immunity [17]. A comprehensive study of nearly 210,000 critically-ill patients showed high adjusted relative risk for eight clinical conditions (four of which included the respiratory system) for CMV alone or in conjunction with a bacterial infection, see Table 2 [63]. Contrary to expectation, adjusted risk for CMV alone was usually higher than for bacterial infection alone.

A recent search of Medline for hospital case reports covering CMV infection gave over 1,000 papers. A search of EMBASE gave a similar number with less than 10% duplicates. The online resource www.casesdatabase.com identified that 70% of CMV case reports in their database were for patients under the age of 50. There is a clear clinical bias regarding the role of CMV in disease given that it is widely recognized that active CMV infection is prevalent in the elderly [6,16-17,36]. The following literature review regarding the potential effects of CMV in respiratory infections therefore needs to be viewed from the perspective that clinicians are potentially missing an important role for this virus in the elderly.

3.4 CMV and Mortality

The specific effects of the 2012 event leading to higher deaths in those with neurodegenerative diseases and the potential role of CMV have been discussed elsewhere [20]. With respect to the reduction in mortality observed in Fig. 1 for those aged below 65 years it is of relevance to note that CMV appears to promote heightened immune surveillance in the youth to middle age [64-65], conferring protection against respiratory conditions [66], whist in older age the heightened surveillance extracts a toll with declining response to influenza vaccination [67-68], lower immune surveillance against other pathogens [69-70] and increased levels of immune-sensitive illness such as type 2 diabetes, coronary heart disease, pre-frailty, frailty and death [68-71]. Given the focus of this study on respiratory mortality, it is apposite to consider the literature regarding the wider effects of CMV on *all-cause* mortality in general, and then more specifically upon respiratory mortality.

A study on elderly Latinos with CMV IgG in the highest quartile showed fully-adjusted all-cause mortality 1.43-times higher than for those without CMV [72]. The relationship with mortality was largely mediated by interleukin-6 (IL-6) and tumor necrosis factor (TNF). A sample representative of the U.S. population showed that CMV seropositive individuals had 1.19-times higher all-cause mortality while those also with high levels of C-reactive protein (CRP) had 1.3-times higher all-cause mortality [73]. A study of older women gave adjusted odds ratios for those in the highest CMV IgG quartile combined with the highest IL-6 tertile of 3.3 for pre-frailty, 5.2 for frailty and >2.8 for mortality [71].

There are two studies which specifically mention respiratory deaths. A study for residents in Norfolk, England gave hazard ratios for death in CMV seropositive persons of 1.23 (other

causes excluding CVD and cancer) which increased for the quartile in the high IgG group to 1.35 [74]. Of the 'other causes' group 12% of deaths were due to *respiratory diseases*, 16% were gastrointestinal and 21% were central and peripheral nervous system. This study did not demonstrate any association with CRP levels. The higher proportion of nervous system deaths appears to correspond with the higher percentage increase in deaths due to the dementia group also observed during the 2012 event [20]. The final study for residents of Cambridgshire and Nottingham in England gave hazard ratios of 1.21 for respiratory deaths. This study also noted that the proportion CMV seropositive peaked at age 75-79 and was progressively lower in the 80-84 and the 85+ group due to the generally earlier death of those who were CMV seropositive [75]. This conclusion is supported by European studies which showed that the oldest old are either CMV seronegative or have a strict pro-inflammatory response to CMV pp65 and IE1 antigens indicating the virus is under strict immune control [76-77] and have preserved glucose metabolism [78]. The issue of preserved glucose metabolism appears important regarding pneumonia survival [79] and survival among the critically ill [80].

It has also been proposed that the sensitivity of certain individuals to the deleterious effects of CMV in old age may be related to genetic factors. For example, different strains of mice show marked differences in CMV infection of the lung and for interstitial pneumonia, and also show widely different ratios for CMV load in the lung versus the salivary gland [81]. In humans a variety of gene variants influence susceptibility to different types of CMV disease [59-60,82-84] among which are genes regulating respiratory health [16-17]. Least sensitive are those elderly able to maintain T cell mediated immune function via an active thymus [49,85], a trait which is probably genetically sensitive. These CMV-specific relationships among the oldest old are likely to explain the markedly lower increase in deaths for the 95+ group seen in Fig. 1.

Depending on the duration of the above studies, they will overlap with a number of these presumed outbreaks. On most occasions, there are two outbreaks per decade, except in the 1990's when there were up to four outbreaks, although in the UK, two of these appeared to be more regional than national. Outbreaks in the US appear to lag by around one year after those seen in the UK, although this lag may be partly due to spread across a far larger geography [13]. The fact that CMV increases all-cause mortality is another pointer since the increase in death during the 2012 event was spread across a wide variety of diagnoses [86], as is the increase in hospital admissions [4,6,15].

The issue regarding CRP is worthy of passing mention as a potential marker for CMV. In renal transplant recipients it has been noted that CMV infection elicits a consistently *lower* CRP response than for tuberculosis or general bacterial infection [87]. CRP is produced in the liver mainly in response to IL-6 while it has been noted that CMV tends to elicit an IL-10 response which is counterbalanced by IL-10 mimicry [6,44]. Hence studies (above) noting high IL-6 and/or CRP are probably detecting instances of the altered balance between pro-inflammatory and anti-inflammatory forces along with potential dual chronic bacterial/CMV infection (for CRP), perhaps facilitated by CMV immune suppression.

3.5 CMV and the Lung

The lung is the most common organ acting as a CMV reservoir apart from blood leukocytes [88-91] and is a common source of respiratory diseases especially in transplant recipients [92]. Frequency of detection in organs is double the average in cases of leukemia and lymphoma [88]. CMV DNA is commonly detected in higher levels in broncho-alveolar lavage

cells than in blood leukocytes even in healthy subjects [90]. Another study suggested that tracheal aspirates (as opposed to blood serum) were the preferred method for determining earlier diagnosis and final clearance [93]. Peak DNA load in tracheal aspirates have been observed to be higher in those with undetectable levels of CMV pp65 and IE-1 specific IFN-γ CD8+ and CD4+ T cell subsets [94].

In vivo, lung fibroblasts, epithelial cells, endothelial cells and smooth muscle cells and macrophages are commonly infected. Alveolar epithelial cells are a main target resulting in detachment from the basement membrane [89]. This tissue specificity for CMV within the lung is highly relevant to the observed large increase in death due to bronchiectasis (J47) seen in Table 1. Bronchiectasis is the irreversible dilation of part of the bronchial tree caused by destruction of the muscle and elastic tissue (both CMV targets) and leads to the accumulation of mucus which can become a focus for bacterial infection. CMV infection of lung fibroblasts leads to cell cytoskeletal disorganization due to actin depolymerisation which further facilitates viral infectivity [95]. CMV infected fibroblasts exposed to IL-8 (a contributor to inflammatory diseases) show enhanced virus replication and production with CMV also selectively inducing transcripts of IL-8 type 1 receptor [96]. In mice CMV infected macrophages show marked inhibition of *S. aureus* phagocytosis [97] while CMV infected human macrophages also show inhibition of respiratory burst when exposed to *P. carinii* which was reduced even further in conjunction with exposure to hydrocortisone, an anti-inflammatory agent which is a known risk factor for CMV re-activation [69].

There is a wealth of evidence pointing to an active role for CMV in respiratory infections in children and older adults. In younger children, a selective deficiency of CD4 T-cell immunity toward CMV leads to persistent viral shedding [98] and renders them sensitive to wider CMV-disease. Hence a study in Taiwan demonstrated that for viral upper respiratory tract infections in children CMV was the cause on 5% of occasions, however, this proportion was far higher in children aged less than five years [99]. In otherwise immunocompetent children admitted for suspected infectious mononucleosis the occurrence of multipathogen infections was 68.9%, 81.3% and 63.6% in the children with primary EBV, CMV or EBV/CMV, respectively, which was significantly higher than in the past-infected or uninfected group. In the multipathogen-infected patients, the incidence of *Chlamydia pneumoniae* was around 50%, significantly higher than in the other groups [100]. In a prospective study carried out in Lyon, France, the association between the excretion of cytomegalovirus (CMV) and the increasing frequency and severity of viral respiratory infections in children attending day-care centers was evaluated. Viral acute respiratory infections were significantly more frequently recorded in day-care centers in which CMV and respiratory viruses co-circulated, and were significantly more frequently reported in CMV-infected children. These findings suggest that viral acute respiratory infections are significantly more likely to occur in CMV-infected children [101]. The large increase in typical childhood (usually aged below 2 years) hospital admissions (typically around 12% to 14%) for conditions such as tonsillitis, asthma, common cold and bronchiolitis seen in Table 3 can be viewed in this light. Hospital admission for infants (aged less than 1) in Northern Ireland (NI) has also been demonstrated to show peaks following the 2003 and 2008 events, although in both cases while deaths in the UK peak in 2003 and 2008 the outbreak in NI commences in mid-2002 and -2007 [6].

In both the elderly and respiratory intensive care units (ICU), CMV infection is frequent in mechanically ventilated critically ill patients, especially for those who are elderly. It is associated with poor outcomes, leads to increased mortality and morbidity in terms of increased ICU stay, longer duration of mechanical ventilation, and higher rates of nosocomial infections [102]. The effects of age have been highlighted in Fig. 1. With respect

to the increased female deaths from asthma noted in Table 1 it is relevant to note that in allergic asthma patients the number of activated CD8+ T cells are significantly reduced in CMV seropositive patients [103].

CMV is not the only agent to infect the lung and herpes virus DNA was detected in 97% of cases of familial or sporadic pulmonary fibrosis. Epstein Barr virus (EBV) and CMV were the most commonly detected, however, different herpes viruses appeared to be more common in different types of this disease and causation was heavily implicated [104], i.e. CMV is more likely to be associated with certain types of pulmonary fibrosis and the incremental change in deaths observed to occur in 2012. Another study of IPF patients demonstrated that CMV DNA copy number was higher in the blood leukocytes and serum than that seen in the control group [90]. However it is of interest to note from Table 1 that J84.1 (interstitial pulmonary disease with fibrosis) and J84.9 (unspecified interstitial pulmonary disease) was one of the respiratory conditions showing an increase in deaths during the 2012 event, especially among women. CMV re-activated mice show increased pulmonary fibrosis with ganciclovir preventing both re-activation and fibrosis [105].

In England, the causative agent for pneumonia is poorly determined hence ICD code J18 (organism unspecified) accounts for over 99% of J12-J18 (all pneumonias), hence, Table 1 can only be said to indicate that a pneumonia-like illness showed an increase in deaths in 2012. In one study of 1,356 patients with life-threatening pneumonia requiring admission to intensive care (and hence with confirming tests) only 34% had a bacterial etiology [106]. This poses the interesting question regarding the remaining 66% of potential life-threatening non-bacterial pneumonias. On this occasion uncomplicated bacterial pneumonias are directly amenable to antibiotics and are therefore less likely to be life threatening.

CMV pneumonia (pneumonitis) is a rarely reported condition, however, of 12 case reports three patients receiving ganciclovir all survived while 60% of those not receiving antiviral treatment died [107]. To explain the large increase in pneumonia death (after inclusion of the dementia group) it is important to point out that during the 2102 event 50% of female deaths were aged 84 and above and it is highly likely that no one was looking for evidence of CMV infection in this age group and had assumed a bacterial etiology. It is important to note that CMV PCR in the blood of those with CMV-pneumonia is usually *negative* and that diagnosis usually relies on elevated IgM/IgG [107]. In mice CMV promotes (but does not cause) the development of interstitial pneumonitis, the severity of which is related to the burden of virus replication [108].

The possibility that CMV plays a hidden role in pneumonia, especially in geriatric patients, is illustrated in a study of nosocomial infections in an elderly rehabilitation unit [26]. Of the 39% of patients acquiring a nosocomial infection within three months of admission some 53% had acquired pneumonia or bronchitis. This group had the highest level CMV seropositive (87% versus 78% in those not acquiring an infection) but also had the highest proportion of individuals with an immune risk phenotype (IRP), a group of immunological changes which are associated with end-of-life. A positive IRP is usually the result of a lifetime exposure to CMV but where immune control is poor. Some 38% of those with a lung infection had an IRP positive profile compared to 21% in those who did not acquire an infection. In-hospital mortality was highest in the pneumonia group (18% versus 3%). Unfortunately IgM and IgG measurements for active CMV infection were not performed but IRP positive plus higher CMV seropositivity is highly suggestive of active CMV infection in the pneumonia group along leading to the high in-hospital mortality.

The central point to these issues is that CMV can enter the body via multiple routes and can establish 'hidden' pockets of infection in multiple organs/cell types and serological, virological or PCR DNA in blood alone may be insufficient. From a technical viewpoint PCR detection of CMV DNA in blood should be conducted on whole blood rather than plasma [109]. Indeed in the intensive care setting 23% of patients were observed to have CMV DNA only detected in tracheal aspirates with serum being negative [93] while in lung transplant patients CMV DNA was always higher in bronchoalveolar lavage and copy number increased with CMV-induced morphological changes [110]. Of relevance to this issue is the fact that during CMV-mediated flares in inflammatory bowel disease CMV DNA is frequently *not* detected in the blood. However, CMV-specific CD8 effector T cells which contain perforin (PFN) and granzyme B (GzB) in their cytoplasmic granules are present in far higher frequencies than in healthy controls [111]. This is illustrative of the ability of CMV to 'hide' in various organ/tissue compartments and explains why blood (as a separate compartment) is not always the best place to search for evidence of active CMV infection of specific organs such as the lung. Further studies on pneumonia in general and during these outbreaks measuring CMV-specific CD8 effector T cell activity is therefore warranted. Finally, high serum glucose levels are predictive of death for community acquired pneumonia [79] and the previously mentioned role of CMV in this area requires further study.

3.6 CMV and Gender

Both in this study and that dealing with neurodegenerative conditions [20] a general higher increase for females in a range of conditions can be seen. J60 (coal dust) and J61 (asbestos) are obvious exceptions due to almost exclusive male occupational exposure. The chronic inflammation afforded by these agents could then be exploited by any major outbreak involving the lung. However the overall female-oriented response is also observed in medical admissions during these outbreaks along with a curious selection against the female fetus [10] and has been attributed to differences in the immune response in females, perhaps due to the specific immune requirements needed to support pregnancy. This is further augmented by generally higher levels of CMV seropositive seen in females at an earlier age than men [6,16]. The distinction between the genders deserves far greater attention in further studies on this topic.

3.7 Multiple Strains of CMV

It is important to realize that CMV operates via multiple strains of differing clinical significance [6,16]. In the mouse, CMV strains are able to act co-operatively at the level of a single cell [112] and this co-operative action appears to lie behind the greater clinical severity observed in multi-strain infections [6,16]. One possible explanation for the increase in deaths could be the emergence of a new strain. The evidence for outbreak-like undulations in the proportion CMV seropositive has been recently reviewed [6] and two additional Australian studies are relevant. In both studies large peaks in the level of hospitalization for congenital CMV infected infants and young children and for CMV disease in HIV/AIDS were observed to occur around the years 1993/94 and 1997/98 [113-114]. Both of these dates are known to be associated with outbreaks of this agent [13]. Another study in Iowa, USA on congenital CMV infection pointed toward higher infection in some years than others [115]. Hence infectious like-outbreaks of CMV, probably due to a new strain, seem possible and require further investigation.

3.8 Implied Infection Rates

The percentage increases detailed in this study are an underestimate of the full extent of the increase in deaths. Some 22% of local authorities in England and Wales experienced initiation of the outbreak during 2011 while a further 3% did not occur until 2014. Hence deaths (and admissions) in 2011 are already elevated while the 12 to 18 month period of increased deaths leads to possibly greater than a 50% under-estimation of total deaths compared to those reported in 2012 [13].

Deaths are the pinnacle of a morbidity/mortality pyramid and the 10-fold higher increase in the number of respiratory admissions in Table 3 is indicative of far wider effects against human health. Indeed this is confirmed by the fact that the majority of growth in respiratory admissions in Fig. 3 occurs during the outbreaks. This is in contradiction to the previously held assumption that growth is largely driven by the ageing population or demographic change [116]. Indeed Fig. 3 contains the suggestion that admissions may even decline in the long-term if these outbreaks could be prevented. Clearly whatever is happening is having a profound effect on health and health care costs and should in no way be trivialized.

The wider effects of CMV against respiratory morbidity were reflected in a study of non-life threatening CMV infections conducted in the period before the 2003 outbreak in the Cambridge and Chelmsford area of the East of England. This study excluded those with hematological and oncology conditions, transplant recipients and receiving immunosuppressive medication. In those with CMV-mediated illness (most commonly aged 20 to 40 years), 28% reported respiratory symptoms although this jumped to 39% for those who were hospitalized. Of interest was the fact that there were 5-times more patients consulting a GP for a CMV-mediated persistent illness (mean 8 weeks up to 32 weeks) with symptoms of malaise, fever, sweats, pyrexia and abnormal liver function test results) than for those who was hospitalized [117]. Not a single patient was diagnosed by their GP as having a CMV-mediated illness with most common GP (syndromic) diagnoses of hepatitis (28%), viral illness (22%), glandular fever (21%), influenza-like illness (13%), and potential malignancy (6%).

Despite the narrow focus of the above study (average age of 40 years) it did identify that in the period before one of these outbreaks 1.63% of those tested had CMV IgM >300 U/mL, i.e. an active CMV infection. Assuming that the outbreaks are due to a new strain of CMV which will immediately establish an active infection, and estimating a maximum possible 60,000 deaths (of which 20% are respiratory) over the entire duration of the outbreak [13], which are restricted to those aged 65+ in a population of 7 million aged 65+ in England (in 2011), gives a maximum death rate due to the infection of 0.7% in this age group. In this age group there appear to be roughly 4 respiratory hospitalizations per death (after adjusting Table 3 for the proportion of admissions over 65 years). If we assume that all of these were hospitalized prior to death this gives a 2.8% infection rate for hospitalization and death. Using the rough ratio of 5:1 hospitalized: GP consulted (determined above) gives an approximate maximum overall population infection rate of 9% occurring over the period of the outbreak. The CMV hypothesis is therefore within feasible limits and the implied infection rates are well within those established in the review of Hyde et al [118], especially given the respiratory involvement identified in this study and the known transmission of CMV from children (the most likely ‘carrier’ group) to their grandparents [119-120].

The author is currently drafting a study of the digestive system diagnose which increased in 2012 in parallel with respiratory and neurological deaths. Once again, diagnoses associated

with increase death are characterized by known associations with CMV infection (in preparation). Hence, for the moment, the CMV hypothesis (either infection with a new strain or re-activation due to another agent) remains a credible possible explanation for an enigmatic phenomena.

4. CONCLUSION

In ageing populations, especially age 65+, a mix of immunosenescence, inflammageing, increasing prevalence of vitamin D deficiency and (in some) a lifetime exposure to the erosive effects of CMV upon immune function create the opportunity for enhanced death during epidemics of immune modulating agents, of which CMV is one of the most prevalent. Those with diabetes (or pre-diabetes), low levels of vitamin D or taking anti-inflammatory medication are at increased risk. A recurring series of such epidemics can be discerned, of which the 2012 event in England and Wales is an example. Death as an outcome occurs in less than 0.7% of the elderly population with up to 9% experiencing a range of symptoms for which they may consult a GP while 3% may be hospitalized. CMV appears to be involved in some way, either via the introduction of a new strain or via re-activation in response to another infectious agent. The issue of pneumonia or a pneumonia-like illness requires further detailed investigation. Whatever the exact etiology it is clear that a respiratory phase is part of the modus operandi of infectious spread for this agent and consequent increased death. Given the profound impact on increased death, associated hospital admissions and wider health care costs the search for the exact agent needs to become a priority.

CONSENT AND ETHICAL APPROVAL

It is not applicable. All data is publically available.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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