Is Cytomegalovirus Involved in Recurring Periods of Higher than Expected Death and Medical Admissions, Occurring as Clustered Outbreaks in the Northern and Southern Hemispheres?

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Review Article

ABSTRACT

A series of clustered infectious-like events have been recently documented in both the northern hemisphere (Canada, UK [England, Northern Ireland, Scotland and Wales], all countries in the European Union, and the USA) and the southern hemisphere (Australia and New Zealand), in which both deaths and emergency admissions for a range of medical conditions appear to simultaneously rise in a step-like manner, stay high for a period of 12 to 18 months, and then revert back to the expected time trajectory.

These unique events are also observed in very small geographical areas within the population area of a single hospital or Primary Care Organisation (PCO), and this precludes explanations based on acute thresholds to admission or to PCO funding, procedures and practice. These events have been overlooked by traditional health surveillance methodologies, simply because it was assumed that neither deaths nor medical admissions could behave in this unique way. Indeed, in the UK it has been widely assumed that the increases in medical admissions arising from these events are solely due to deficiencies in the organization and delivery of health and social care, often labelled as 'failure to manage demand'.

Based on the spectrum of medical conditions which are associated with the increased admissions

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and deaths, it has been proposed that the ubiquitous herpes virus, cytomegalovirus (CMV), may in some way be associated with these outbreaks. This involvement could be either by (re-)infection with a new strain, or by opportunistic reactivation in the presence of another agent. This review will examine if CMV is indeed capable of causing substantial increases in both deaths and medical admissions, and which conditions in particular would be affected.

1. INTRODUCTION

Firmly held assumptions regarding the way in which the world is supposed to behave can become codified into professional practice, but at the same time can become a huge hindrance should one or more of those assumptions prove to be incorrect. The earth is flat, or the earth is the center of the solar system, are two historical examples. A more recent example has been the observation that both the time trend for deaths and medical admissions are not behaving in the way that they are 'supposed to' or 'ought to' behave.

Over 20 years ago this author was a senior manager at a large UK hospital when medical admissions suddenly jumped by 13% in the middle of March 1993 and stayed high for many months. None of the hospital processes or procedures had been changed, and there had been no corresponding changes in primary or social care [1]. This same event was observed across the whole of the UK, see review [2], and was associated with a corresponding jump in deaths which stayed high for the following 12 months [3]. This was repeated again in 1996, 1999 and 2002, and led to a host of studies investigating the apparent rampant growth in emergency admissions [see 2]. At that time no one thought to investigate the possibility of spatial spread, and in the absence of this key factor, it was assumed that the unexplained increase in admissions was due to a wide range of factors relating to 'inefficiencies' within health and social care [see 2]. This assumption then became codified, as academics quoted other academics in studies showing that certain factors may be associated with higher admissions – although an association with higher utilization does not explain higher growth *per se*.

Recent very small area studies, have categorically demonstrated that the increase in medical admissions spreads in an infectious-like manner within the catchment area of a single hospital or a single Primary Care Organization (PCO), and that this infectious-like spread occurs slowly in a manner expected from a relatively difficult to transmit agent [4-6]. Studies on deaths, GP referral and occupied hospital beds using local authority geographies across the whole of the UK have replicated the same observations [1,7-12], as has spread across Europe [2], Australia [13] and New Zealand (in preparation).

A number of studies have now established the following features for these events:

a. Can be traced back to the 1950's, usually twice per decade but sometimes more often [3].
b. International in scope [2,12].
c. Involve a specific range of conditions / diagnoses with an apparent immune function basis (infection, inflammation and autoimmunity) [1,14-32].
d. Are age and gender specific, although the effect is largely against the elderly [14,19,33-38].
e. Appear to trigger a small change in the gender ratio at birth [39].
f. Involve a simultaneous increase in all-cause mortality, emergency medical admissions [7,14,40-42], and emergency department attendances [9].
g. Also involve increases in sickness absence [43].
h. Are associated with variable increases in GP referral for an outpatient consultation, and alter the ratio of follow-up to first outpatient attendances [10,16,34,38,44].
i. Initiate more commonly (but not exclusively) in the winter months [2,6].

It is clear from the above studies that a biological agent is probably involved, but how do we go about identifying potential candidates? Before addressing this issue, the direct linkage between the spread of increased deaths and admissions needs to be established.

2. SIMULTANEOUS SPREAD OF ADMISSIONS AND DEATHS

While numerous studies have demonstrated the spatiotemporal spread of deaths, medical admissions and GP referral for an outpatient consultation [4-6,9,45-47], and a spatiotemporal link between deaths and admissions has been inferred [47]. It is important to show that the unexpected and sudden increases in deaths and admissions occurs *simultaneously* as part of wider spatiotemporal spread. This section presents previously unpublished analysis of the spread of deaths and medical admissions across Northern Ireland using 26 District Council geographies.

In a genuine infectious outbreak deaths are likely to peak later than admissions, since initial illness precedes eventual death. In this study, only financial year data (April to March) was available for medical admissions for residents of each of 26 relatively small District Councils between 2000/01 and 2013/14. In this interval, there were four potential outbreaks with deaths peaking around 2003, 2008, 2010 and 2012. The dates cited for each event are the calendar year in which deaths peak across the UK. However, monthly deaths were available for each District Council, which could be summed to give total deaths for the 12 months ending in any month of the year, including a financial year.

The fact that deaths show relatively slow (and granular/heterogeneous) spatial spread is illustrated in Table 1, which lists the date of initiation and the percentage value of the step-like increase for both the 2010 and 2012 events. Spatiotemporal spread for the 2010 event occurs between Jan-09 to Dec-10 (Mar-10 as median), while that for the 2012 event occurs between Aug-11 to Dec-12 (Apr-12 as median). Average deaths per annum (p.a.) are shown for each District Council to indicate that they are mostly small areas (except for Belfast), and a standard deviation (Poisson) is also given to show that the percentage increase cannot be due to chance, except in a minority of cases (mainly associated with the 2010 event). A full description of methods is available in the paper by Jones & Beauchant [6].

While these events do not occur exactly in line with financial year-end, there is sufficient clustering of initiation around March (a suspected winter preference for infectious spread) to enable paired comparison of year-on-year changes in medical admissions with changes in deaths. Measured over five of the outbreaks, initiation of the step increase in deaths in February and March was most common (28% of occasions compared to 17% by chance), and this is similar to that observed across Europe [2].

A potential lag between admissions and deaths was determined by comparing the percentage change in admissions and the percentage change in deaths at April, May and June rather than March (financial year end). The absolute difference between change in admissions and deaths was summed to determine in which month the sum of the absolute differences reached a minimum. This sum was seen to reach a minimum at a one month lag but was only slightly higher for a two month lag. This indicates that the lag is closer to one month (say five to six weeks). The sum of absolute differences for a three month lag was much higher, indicating that this lag was too high.

Having established that there is a one to two month time lag between admissions and deaths, both the one and two month lagged data were used to match the changes in admissions and deaths, and this is presented in Fig. 1 where each data point represents the average step-change in admissions in each of 40 equally spaced bins representing a 1% increment in the percentage change in deaths.

In Fig. 1 a large positive change in deaths and admissions will occur mainly when the step-change occurs close to financial year-end, while negative values occur in the period when admission and deaths revert back to baseline levels around 12 to 18 months after initiation, leading to a step-down. Small changes tend to occur in the 9 out of 13 years when there are none of these particular kind of infectious events. Deaths show larger percentage changes because they are smaller numbers. Also note that the effect of each outbreak leads to differential effects upon morbidity and mortality, and hence Fig. 1 is an average of the relative effects between morbidity and mortality. Each outbreak therefore probably lies on a series of lines parallel to that in Fig. 1. Having established that large increases in deaths and medical admissions occur as synchronous spatial spread, we can now evaluate a potential candidate for these outbreaks.

Table 1. Month of initiation and percentage increase in deaths associated with two infectious-like events spreading across Northern Ireland

District council	Average deaths p.a.	Standard deviation (Poisson)	2012 event		2010 event	
			Increase	**Initiation**	**Increase**	**Initiation**
Ards	670	3.9%	10.7%	Jul-12	14.0%	Feb-10
Belfast	2,970	1.8%	7.7%	Aug-11	1.9%	Nov-10
Castlereagh	640	4.0%	8.8%	Dec-12	6.8%	Jul-10
Down	550	4.2%	6.9%	Nov-12	5.3%	Aug-10
Lisburn	840	3.4%	10.5%	Jun-12	9.3%	Sep-10
North Down	770	3.6%	10.5%	Sep-12	3.6%	Dec-10
Antrim	370	5.2%	15.0%	May-12	11.9%	Jan-09
Ballymena	540	4.3%	21.7%	Nov-12	16.5%	Aug-10
Ballymoney	220	6.7%	26.5%	Nov-12	11.5%	Mar-10
Carrickfergus	330	5.5%	2.7%	Nov-12	18.4%	Sep-09
Coleraine	490	4.5%	13.0%	Feb-12	9.1%	Aug-10
Cookstown	260	6.2%	22.8%	Feb-12	11.7%	Feb-10
Larne	290	5.9%	18.4%	Aug-11	14.5%	Oct-09
Magherafelt	280	6.0%	11.0%	Oct-12	26.8%	Aug-10
Moyle	150	8.1%	13.8%	Oct-11	20.3%	Oct-09
Newtownabbey	690	3.8%	8.4%	Apr-12	12.3%	Jun-10
Armagh	460	4.6%	10.2%	Dec-11	12.8%	Feb-09
Banbridge	330	5.5%	30.8%	Nov-12	14.2%	Feb-10
Craigavon	650	3.9%	13.4%	Apr-12	3.2%	Jun-10
Dungannon	410	4.9%	12.2%	Mar-12	13.3%	Mar-10
Newry &Mourne	690	3.8%	11.8%	Jan-12	18.1%	Mar-10
Fermanagh	540	4.3%	15.1%	Jul-12	6.1%	Nov-10
Limavady	220	6.8%	22.4%	May-12	16.2%	May-09
Derry	770	3.6%	8.7%	Dec-11	9.7%	Sep-09
Omagh	380	5.2%	14.4%	Oct-11	13.0%	Jan-09
Strabane	300	5.8%	7.9%	Jan-12	15.6%	Oct-10

In a Poisson distribution a + 1 standard deviation change represents 85% of all possible outcomes, i.e. the 85% confidence interval. Monthly deaths in the 26 district council areas of Northern Ireland were obtained from the Northern Ireland Statistics and Research Agency (NISRA) website
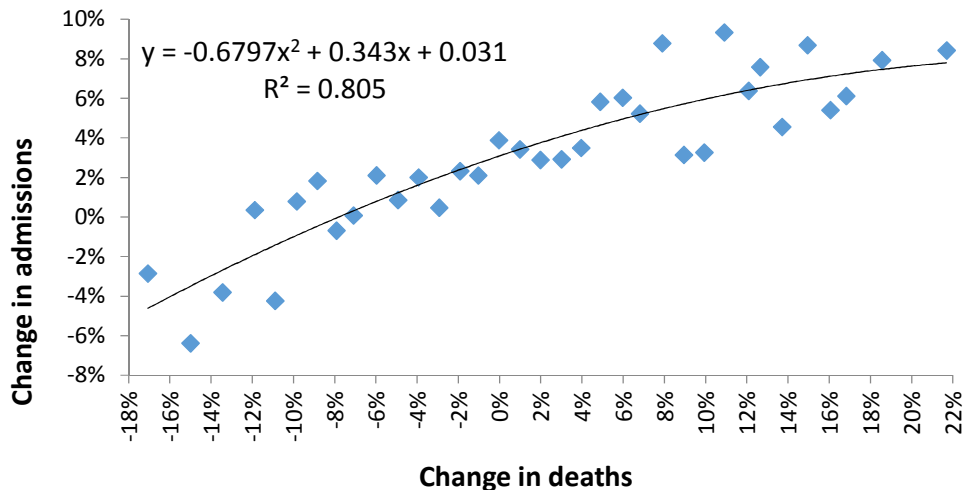

$$y = -0.6797x^2 + 0.343x + 0.031$$
$$R^2 = 0.805$$

Fig. 1. Linkage between spatiotemporal spread of deaths and admissions for 26 district councils in Northern Ireland between 2000/01 and 2013/14
Medical group admissions include general and elderly medicine (approx. 70%), cardiology (approx. 20%), Gastroenterology, rheumatology, etc (approx. 10%). Medical admission data kindly provided by the Northern Ireland DHSSPNI

3. A POTENTIAL AGENT

Since these events have been missed over many years, it is highly likely we are looking for a common infectious agent which is regarded as being of little clinical effect. The agent must cause a persistent infection to explain the enduring effect on deaths and admissions, and must provoke an immune response to account for the repeating pattern of outbreaks [3,48-52]. Agents such as gonorrhea can be excluded since they do not provoke an immune response and therefore do not show periodicity in occurrence [51-52]. The agent will have a very large genome in order to code for the multitude of proteins implied by the cluster of immune modifiable diseases which peak during the outbreaks.

Based on the above the most likely candidate is the ubiquitous herpes virus, cytomegalovirus (CMV) [1]. The key features relating to this virus are as follows:

a. Has the largest genome of all herpes viruses, and can code the equivalent to 3% of the entire human genome via orchestration of the expression of over 8,000 cellular proteins [53-54]. Both mid-frame and reverse frame transcription enhance the number of coded proteins [53-54]. Only 25% of the genome is highly conserved. A total of around 860,000 single nucleotide polymorphisms (SNPs) across 154,000 sites on the genome lead to abundant strain diversity [55].

b. This huge repertoire of proteins and mRNAs is largely unstudied.

c. Exists as a huge variety of strains with multiple variants in the genome and the glycoprotein coat [55,56].

d. Causes overt infection in a minority of cases (including the fetus during pregnancy), but other than that is largely considered clinically insignificant (despite the widespread immune disruption implied by the large genome) [56-57].

e. Individuals can be re-infected with a different strain (up to 7 strains per individual) giving room for recurring outbreaks [see 1].

f. Multi-strain infections are synergistic and lead to the most severe clinical outcomes [see 21,29].

g. Infection of a cell leads to elevated metabolic activity which stimulates the replication of some RNA viruses [58], i.e. the basis for increased admission for certain other infections.

h. Widespread disruption of both innate and adaptive immune function is known to occur [59-66].

i. Immune subversion occurs even during latency [67-68].

j. Almost all cell types (including immune system myeloid lineage cells) can be infected although in some this is restricted to a non-replicative infection [1,69] – which can be immune modifying, as in "i" above.

k. Is most effective in situations of impaired immunity including HIV/AIDS or ageing [70] - the latter concurs with the typical older ages for those who die or are admitted.

l. Has been confirmed to be oncogenic for particular cancers and oncomodulatory in others [71-88].

While this has not been conclusively established, it is highly likely that CMV immune disruption is leading to enhanced disease progression in the cluster of conditions observed to increase during the outbreaks.

3.1 CMV and Inflammatory Markers

Throughout this review reference will be made to various inflammatory markers. Among the most common are interleukin-6 (IL-6) and C-reactive protein (CRP). CRP is an annular pentameric protein found in blood plasma. CRP is synthesized in the liver by hepatocytes and levels rise in response to inflammation, specifically to IL-6. Its physiological role is to bind to lysophosphatidylcholine expressed on the surface of dead or dying cells (and some types of bacteria) in order to activate the IgG complement system via the C1Q complex [89]. CRP has no inflammatory properties *per se* and infusion of pharmaceutical grade human CRP into healthy volunteers is not proinflammatory [90]. CRP is therefore an indirect measure of (certain types of) inflammation. In renal transplant recipients CRP levels varied depending on the type of infection, namely, bacterial (8-383 mg/L), tuberculosis (35-172 mg/L) and CMV (0.3 – 44 mg/L). CRP levels in CMV infection rose depending on the degree of infection, asymptomatic < symptomatic < invasive [91]. Hence CMV is not a strong promotor of CRP, but CRP does increase with the severity of CMV infection.

IL-6 is an interleukin that acts as a pro-inflammatory cytokine [92]. In humans, it is encoded by the IL-6 gene. IL-6 is secreted by T

cells and macrophages to stimulate an immune response, e.g. during infection and after trauma, especially burns or other tissue damage, leading to inflammation. Osteoblasts also secrete IL-6 to stimulate osteoclast formation and smooth muscle cells in the tunica media of many blood vessels also produce IL-6 as a pro-inflammatory cytokine [92]. IL-6 is a potent CMV promotor and CMV also promotes IL-6 secretion by infected cells.

3.2 CMV Operates at Multiple Levels

An area of great confusion regarding the action of CMV lie around its clinical and sub-clinical effects. Observable CMV disease associated with CMV viremia is a relatively rare but potentially life-threatening disease [56-57]. Common symptoms are listed in Table 2, while the age profile for CMV case reports are given in Fig. 2, and age-related incidence in England is given in Fig. 3. The relative infrequency of observable clinical disease has led many textbook's to declare that CMV is therefore a relatively minor pathogen, except in those with known immune deficiencies such as HIV/AIDS, transplant recipients or the fetus. It must also be pointed out that CMV awareness among clinicians in the UK is relatively low, and the age-related incidence for hospitalization in Fig. 3 is probably a gross underestimate. This will be especially so at ages 70+, where clinicians will assume that the illness is due to 'age' or 'an infection' [1]. In this respect CMV reactivation (measured as IgG CMV anti-late, anti-early and anti-intermediate) is far more common in elderly (aged 70+) versus young (aged 25 to 38) subjects [93].

Table 2. Common presenting conditions and symptoms in those hospitalized with CMV-attributable disease

Condition	Cases	Symptom	Cases
Infection	46%	Fever	45%
Lymphadenopathy	20%	Pain	16%
Cough	18%	Inflammation	15%
Headache	11%	Vomiting	12%
Hepatitis	5%	Fatigue	7%
		Abdominal pain	5%

Data for 610 cases was extracted from www.casesdatabase.com using the search terms 'Cytomegalovirus' and 'CMV'. This website is no longer available

Fig. 2. Age and proportion of case reports for confirmed CMV-mediated admissions
Data for 610 cases was extracted from www.casesdatabase.com using the search terms 'Cytomegalovirus' and 'CMV'. This website is no longer available
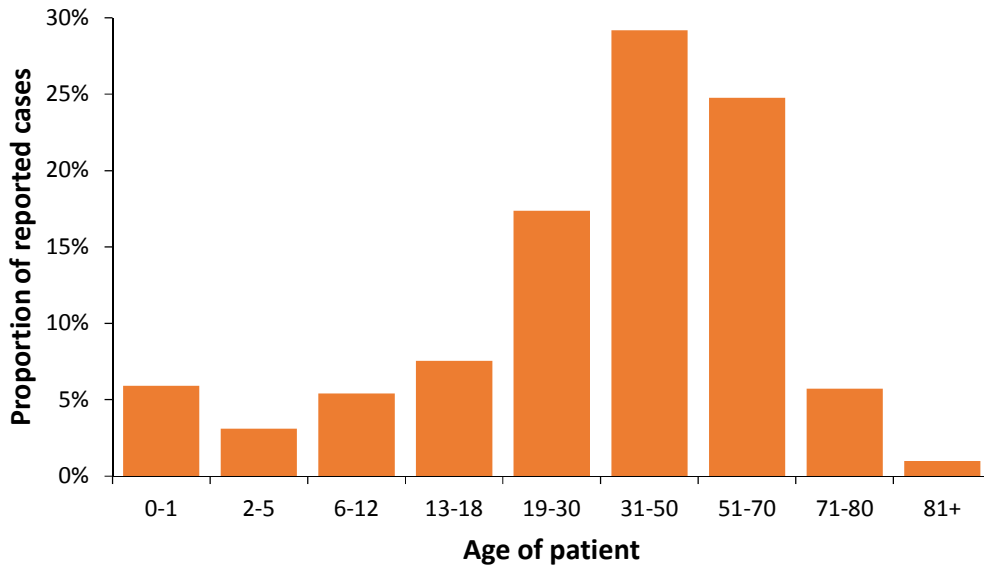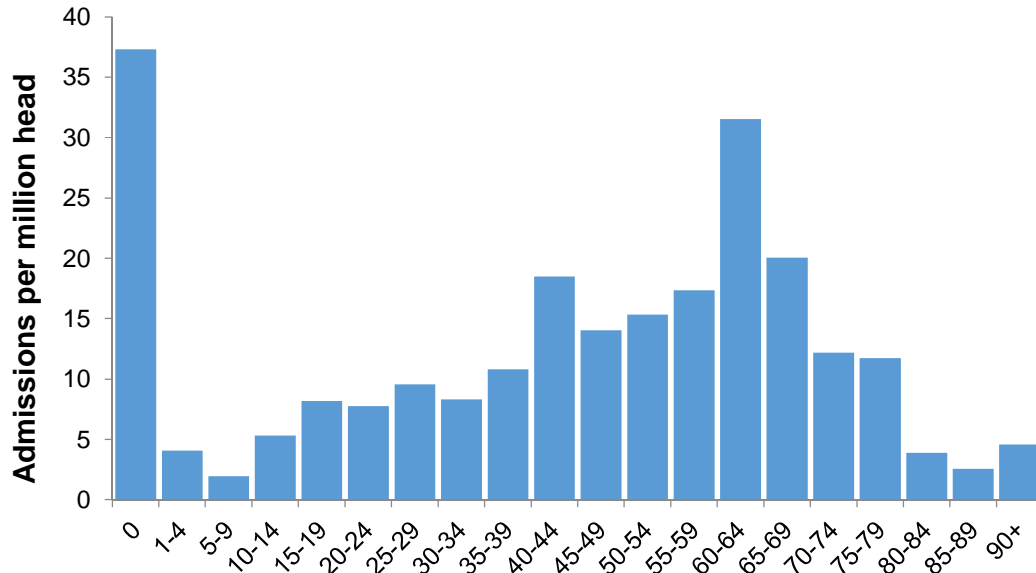
Fig. 3. Rates for hospital admission with confirmed CMV-disease in England, 2012/13
Data is from Hospital Episode Statistics (HES) available from the Health and Social Care Information Centre (HSCIC) website http://www.hscic.gov.uk/

However, observable CMV viremia is only the tip of a much larger CMV disease pyramid. The list of diseases often associated with CMV viremia is however illustrative in that it delineates those body systems where CMV is most active. Evidence for the sub-clinical work of CMV in these areas, and for a similar disease spectrum in the proposed outbreaks, is therefore an intrinsic part of this review. In this respect it has been observed that case reports are a useful tool in identifying and managing emerging infectious diseases [94]. The comprehensive review of Rafilides et al. [56] regarding infection of the *immunocompetent* patient established that CMV is most active in the following clinical areas:

- Neurological and central nervous system (CNS) disorders
- Cardiovascular diseases (CVD)
- Respiratory infections
- Digestive system diseases
- Haematologic disorders
- Ocular uveitis

The work of others suggests that the role of CMV as an oncomodulatory and as oncogenic agent in certain cancers (breast ductal, gliomas, salivary duct, gastric, colon, prostate, cutaneous T-cell lymphomas and perhaps others) should be added to this list [71-88]. The evidence that CMV

is associated with increased risk of death for the above conditions will now be investigated.

4. CMV AND ENHANCED MORTALITY

During the 2012 outbreak in England the maximum increment in the death rate per 1,000 population was + 6 (±4 as 99% confidence interval) which occurred in males aged 86 and females aged 89, however the average for those aged over 75 was +0.7 per 1000 population for males and +1.6 for females [95], i.e. the actual rates are not excessively high and we are therefore looking for an agent with only modest incremental effects upon mortality. The fact that these deaths are spread over a 12 month period, rather than in a single influenza-like peak, partly explains how they have gone undetected for so long. The effects of CMV on enhanced mortality covers three areas, namely, those with known immune deficits, those who are critically ill and those who are relatively healthy. Each will be discussed.

In the area of organ transplantation, CMV is a well-recognized agent for organ rejection and life-threatening infection in solid organ and stem cell recipients [96-97]. CMV is a well-recognized risk factor in those with HIV/AIDS [8], and in one study those who were receiving anti-retroviral therapy but with detectable CMV DNA in the

blood had an 8-times risk ratio (RR) for death [98]. In another study, in those prior to receiving antiretroviral therapy, CMV viremia (CMV DNA above 1,000 copies /ml) was associated with a 2.3-times odds ratio (OR) after adjusting for viral load, CD4 count and disease stage [99]. These authors noted that the CMV viremia had only sub-clinical effects. This is a key observation since reports of observable CMV disease are very rare – yet the virus is associated with very high risk scores. Finally in those with HIV/AIDS stimulation of CD38+ T cells with CMV peptides promotes an inflammatory response which is not replicated for antigens from cleared infections such as tetanus or hepatitis [100].

In autoimmune disease, especially systemic lupus (SLE), there is a higher risk of death in patients with CMV who have received higher corticosteroid dosage or azathioprine usage. Death is associated with a higher number of CMV per leukocyte, higher proportion of associated bacterial infections and higher SLE disease activity score. The cut-off for mortality was around 25 CMV per 5 x 10^5 polymorphonuclear neutrophils (PMN) [101]. In patients with a range of autoimmune disease, CMV counts in blood were elevated in cases of lymphopenia (OR 34.4), SLE (OR 6.7) or polymyositis/dermatomyositis (OR 10.6) [102]. Anti-inflammatory drugs used in immune modifying conditions such as SLE, MS, arthritis, bronchial inflammation, etc are known risk factors for CMV viremia [103].

Patients suffering from cancer or receiving cancer treatment are another known risk group for CMV-associated death [see 16-17], and deaths for cancer patients admitted to hospital are known to be higher during the outbreaks of the new disease [16-17]. One study of children aged 0 to 17 conducted between 1993 and 1999, i.e. covering three outbreaks, found no difference in age-matched levels of CMV and EBV between children without cancer and those before cancer treatment. However after cancer treatment levels of IgG to EBV were 1.2-times more prevalent after treatment while those for CMV were 1.9-times higher [104]. Children who died were excluded from the study. Leukemia patients showed the highest increase in CMV IgG post treatment followed by solid tumor and then lymphoma, the bulk of these being due to primary infection [104]. This confirms that it is the cancer treatment *per se* that presents the greatest risk for CMV infection, reactivation and disease.

For those who are severely ill, CMV reactivation is a well-documented risk factor for death in the intensive care unit [105-108], burns units (90% higher) [109], patients with septic shock and severe sepsis (80% higher) [110-112], and following major surgery [113]. For mechanically ventilated patients with ventilator-associated pneumonia, CMV reactivation (but not herpes simplex virus) was associated with 55% mortality at 60 days versus 20% for those without CMV [105]. In those following major heart surgery CMV seropositive patients had longer mechanical ventilation, longer stay in the intensive care unit (ICU), longer total hospital stay, and suffered 30% mortality versus only 9% in the CMV negative group [113]. Risk factors in the CMV group were diabetes (OR 17.9) and antibiotics at admission (OR 19.4), i.e. mixed bacterial/CMV infection (next section).

The important role of CMV alone or plus bacterial infection for death or complication in the intensive care unit is illustrated in Table 3 [114]. CMV alone has a higher risk of adverse outcomes than bacteria alone, and CMV is generally one of the viruses with the highest risk either alone or in combination with bacteria. The implications of Table 3 to patients outside of the intensive care unit should be readily appreciated, and CMV therefore represents a widespread but largely unrecognized threat to those admitted to hospital.

For those who are not severely ill but elderly, highest quartile levels of CMV IgG antibodies are associated with higher levels of: diabetes mellitus, cardiovascular disease, pre-frailty (RR 3.3), frailty (RR 5.2) and death (RR 2.8) [115]. Reflecting the observations of this review, a number of large international studies have confirmed that CMV is associated with higher risk of mortality; however, this risk is only elevated in the presence of high levels of CMV IgG and/or other inflammatory markers such as CRP.

In a study of patients with angiographically confirmed coronary artery disease (CAD), non-survivors were associated with higher levels of CMV infection (88% versus 74%), and risk of death was highest in those who were simultaneously CMV positive along with high CRP levels [116].

In 13,090 participants from Norfolk, England; increasing CMV IgG levels were associated with a lower proportion that were physically active or educated to final year high school or above,

slightly higher age, more females, increasing prevalence of diabetes, myocardial infarction, stroke and cancer (excluding skin cancer). Average CRP and fibrinogen levels also increased as did systolic and diastolic blood pressure [117-118]. In the high IgG group (10.7 - 20.8 IU/ml IgG), hazard ratios for all-cause mortality were elevated by 23% (19% for those without baseline cancer, myocardial infarction or cerebrovascular accident), while death from coronary vascular disease was elevated by 24%, by 13% from cancer and 35% from other causes. The relatively modest difference between those without baseline disease indicates that it is CMV *per se* that is the risk factor rather than the diseases themselves.

A study of community-dwelling older people with stable cardiovascular disease gave highest mortality in those with highest CMV IgG levels where the pattern for the cause of death was noted to be significantly different [119]. After adjusting for confounders a Belgian study of those aged 80+ showed a HR of 1.64 for all-cause mortality in the 25% of the population sampled which had CMV IgG > 250 IU/ml [120]. This study ran from 2008 to 2012 and therefore potentially encompassed three outbreaks.

A US study of 14,150 subjects aged 25 and older showed a 19% increase in the hazard ratio (after adjusting for multiple confounders) for death due to all-cause mortality in those who were CMV seropositive. Subjects who were CMV seropositive and with high CRP levels had a 30.1% higher risk for all-cause mortality and a 29.5% higher risk of death due to cardiovascular disease (CVD) [121]. Unfortunately CMV IgG was not measured in this study.

As has been demonstrated above, and in studies in the UK and Europe [1-2,6-7,14,40-41], outbreaks of the new disease are associated with large step-like increases in both deaths, admissions and hospital bed occupancy. To illustrate the wider international effects of these outbreaks the value of the largest percentage step-change in each of 466 Australian Local Government Areas (LGAs) over the time period 2002 to 2013 is given in Fig. 4 [13].

During this interval there were four outbreaks of the agent. The usefulness of Australian LGAs is that they range from very small to very large, and cover all types of ethnic communities, large cities through to outback cattle stations, and age structure. All data exceeds the 85% confidence interval (Poisson), and there is a clear power law relationship between size (as average deaths) and percentage increase in death arising from the step-increase (at the start) or step-reduction (at the end) of the outbreaks. This relationship with size arises from the relatively slow spread of the agent throughout the social networks in each LGA. This slow spread leads to the percentage value being underestimated in the larger LGAs since step-up and step-down within the smaller social networks can cancel each other out (see Jones & Beauchant [6] for discussion).
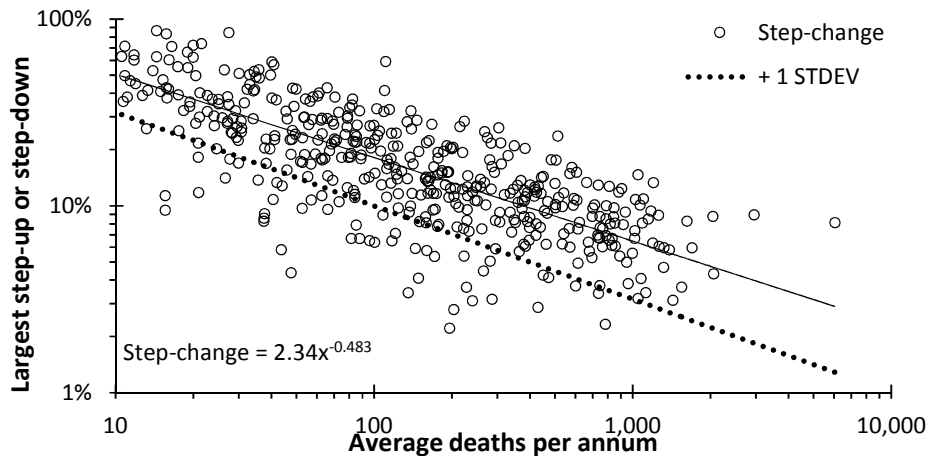

Fig. 4. Largest percentage increase for step-like changes in deaths within 466 LGAs in Australia between 2002 and 2013
Data and methods from the study of Jones [13]. To avoid bias the step-up and step-down percentage values have been calculated relative to the average deaths in each LGA. If the step-like events were due to chance (Poisson) some 85% of the data points should lie below the + 1 standard deviation line (STDEV)

Table 3. Relative risk of death or complication for immunocompetent patients during intensive care

Outcome/Condition	Infection type	Adenovirus	Coronavirus	CMV	HSV	Influenza	RSV	Virus avg	Bacteria alone
Death	Alone			4.21	2.35	*1.55*	11.76	2.36	4.12
	+ Bacteria		9.01	6.66	4.92	2.75		6.58	
Pneumonia	Alone			4.7	3.6	2.1	6.0	2.8	3.0
	+ Bacteria	12.9	4.8	4.3	4.3	*2.2*		3.9	
ARDS	Alone			5.3	2.4	4.2		1.8	1.8
	+ Bacteria			4.2	3.3	3.0		2.6	
Respiratory Failure	Alone			3.6	2.2	3.2	8.4	2.3	2.9
	+ Bacteria	9.1	3.1	4.1	3.9	4.2		4.2	
Diarrhea	Alone			9.8	3.6	3.3		2.9	2.6
	+ Bacteria			6.0	4.8	4.4		4.5	
MSOF	Alone			4.8	2.8	1.5		2.9	5.1
	+ Bacteria			10.1	7.9	5.2		8.3	
Sepsis	Alone		7.0	*7.0*	6.6	4.3		4.0	48.8
	+ Bacteria		65.5	67.5	62.4	45.1		60.0	
Septic Shock	Alone			*21.9*	33.7	*7.5*		11.3	176.3
	+ Bacteria			218.7	309.2	74.6		271.0	

Adapted from Miggins et al. [114]. Avg = Average, ARDS = Acute respiratory distress syndrome, MSOF = Multisystem organ failure, HSV = Herpes Simplex Virus, RSV = Respiratory Syncytial Virus. Numbers in italics have been estimated. Relative risk has been adjusted for age, gender, ethnicity and hospital type

Not every outbreak in each location shows the maximum increase, and Fig. 4 therefore represents a 1 in 11 year largest increase, i.e. it is a demonstration of the maximum potential for the outbreaks. What is clear, is that the agent has a considerable impact on death during the outbreaks. The intercept on Fig. 4 indicates that the maximum impact of the agent leads to a 50% to 100% increase in deaths (although infrequent). However, under optimum conditions and/or along with appropriate mutations or chance additions to the genome, this agent has the potential for almost plague-like outbreaks. In this respect, the possibility of a respiratory phase in the infection has been inferred [22]. Clearly urgent research is required.

The percentage increase in deaths attributable to CMV in the large population-based studies referred to above will be subject to the same degree of underestimation due to the fact that deaths are averaged over longer time periods (covering one or more outbreaks) and due to the spatial effects of the outbreak as observed in Fig. 4. The final issue relating to decease/survival, is the apparent association between the immune risk profile (IRP), defined by an inverted CD4/CD8 ratio and associated with persistent CMV infection and increased numbers of CD8+CD28- cells, and early mortality. Those who survive to 100 appear to have an 'inverted' IRP profile [122].

In conclusion, somewhere around 20% of the population appear to be highly sensitive to the mortality-enhancing effects of CMV, with 20% to 40% increases in mortality in these groups. This author has proposed that thymic output may be a key variable differentiating those who are, and are not, susceptible to the wider effects of CMV [reviewed in 1,21]. In support of this proposal it has been noted that superior survival in the elderly has been correlated with higher frequency of CCR+ CD4+ regulatory T-cells (Tregs) which are involved in maintaining peripheral tolerance to self-antigens [123]. Tregs are trained in the thymus. Likewise both CRP levels and thymic output can be combined to predict likely time to end of life [124], and poor pre-transplant thymic function is associated with the risk of CMV disease after solid organ transplantation [125].

5. CMV AND GENERAL MORBIDITY

On average there are 10 additional hospital admissions per extra death during the outbreaks [47], and it has been calculated that the implied

seroconversion rates are well within the range reported for CMV in the literature [22]. There are numerous studies indicating that CMV is associated with general poor health and disease progression. There are over 100 autoimmune diseases and while not every one of these has been investigated for the involvement of CMV, it is now clear that CMV is implicated in the initiation of a number of the more common autoimmune diseases, in disease progression and symptom severity [28,126]. Roles for CMV in enhanced mortality in autoimmune conditions have been discussed above, and it goes without saying that morbidity precedes mortality.

CMV is also well-recognized in disease mimicry such as hepatitis, polyneuritis, encephalitis, corneal endotheliitis, papillitis and Guilain Barre syndrome, transverse myelitis, Ross syndrome, anemia, dengue, incomplete urinary voiding and urinary retention, to name a few [see references in 28]. Wider roles for CMV in anemia are now recognized [127].

In one study it was noted that CMV positive elderly had enhanced levels of inflammatory markers in blood plasma (Concentration Ratio of the markers for CMV positive versus negative in brackets): TNF-α (4x), IL-6 and Hsp60 (3.3x), Leptin (2.9x), CRP (2.4x), sCD14 (1.6x) and LPS (1.3x). These differences were not replicated in young subjects. Both LPS and sCD14 are measures of microbial translocation from the gut arising from enhanced intestinal permeability [128,129]. Clearly CMV is associated with enhanced inflammation and bacterial challenge in the elderly, which provides a potential explanation for increased hospitalization for various infections during the outbreaks.

CMV has been long recognized as an agent implicated in various cardiovascular diseases including atherosclerosis [130], angiogenesis [131], thrombosis [132], and restenosis after coronary atherectomy [133]. In one study conducted in Norfolk (UK) the risk of incident ischaemic heart disease (IHD) was 22% higher in those with the highest CMV IgG levels [117-118]. The increased production of IL-6 in response to CMV infection may be the actual causative agent in atherosclerosis [91]. See below for more instances of tissue damage. Those suffering from systemic lupus erythematosus (SLE) are noted to have higher levels of both IgG and IgM than healthy controls [134].

In the elderly, those who are CMV seropositive are more likely to have type 2 diabetes

(17% versus 8%), although IgG levels do not appear to be involved [135]. However there are several case reports of the onset of autoimmune type 1 diabetes following an acute CMV infection [136,137] and post-transplant diabetes in renal transplant recipients, is associated with CMV seropositive patients (OR = 9.6) [138]. Direct infection of human pancreatic β cells by CMV leads to the release of IL-6, IL-8, IL-15 and MCP-1, with binding of inactivated virus particles to the cell sufficient to provoke this response. There was no observable inflammation [139]. One study noted that in those with type 2 diabetes, CMV IgG and IgM are observed in the pancreas (mainly in the islets of Langerhans) of 44% of subjects versus total absence in non-diabetic counterparts [140]. In another study all CMV positive type 2 diabetics expressed MCH class II mRNA in the pancreas (40% in the islets) [141]. Hence direct infection of the pancreas is most likely to be the cause of the higher levels of diabetes in CMV seropositive elderly noted above. The mechanism is likely to be autoimmune based. One study noted a strong correlation between CMV in lymphocytes (22% in the with diabetes group versus only 2.6% in the without) and islet cell antibodies [137], and cross reactivity between T cells and autoantigen glutamic acid decarboxylase may be involved [136]. One further route is via infection of the thymus. Infection of the thymic epithelial cells by Coxsackievirus in the mouse initiates a cascade of immune changes which can lead to Type I diabetes [142]. CMV is able to infect the same thymic tissues in humans [1,21] and this potential relationship requires further study.

5.1 Tissue Damage and Functional Disruption by CMV

CMV is able to infect almost all cell types, although in some the infection does not lead to the production of viral particles (see wider discussion on latency in 5.2). Hence, is there evidence to suggest that CMV is leading to tissue damage and/or modified function?

During the 1990's the classical 'owl eye' inclusion bodies were the accepted histopathological proof for CMV infection. The development of sensitive PCR tests for the presence of CMV DNA has subsequently altered this view. For example, in a sample of 11 HIV positive patients, owl eye inclusions were associated with tissues having an average of 50% higher CMV DNA loads than non-owl eye tissues [143]. In this sample, of the 14 organs tested, the adrenals and lungs had the highest frequency of owl eye inclusions, with the lung showing the highest number of owl eye cases at low DNA load. In this respect the lung is a major site for CMV infection [22]. The stomach, liver and lymph nodes showed no owl eye inclusions despite instances of high DNA load [143]. Clearly owl eye inclusions represent only one measure of the spectrum of tissue damage inflicted by CMV, and different tissues appear to show degrees of susceptibility to the formation of owl eyes.

There are over 100 inflammatory conditions of which fibrosis is a sub-set. Fibrosis is the poorly regulated healing of sites of tissue damage, and all herpes viruses including CMV cause fibrosis in a variety of organs [144]. Enhanced collagen synthesis in chronic transplant rejection is a well-recognized role for CMV [145]. CMV is involved in both pulmonary and hepatic fibrosis [146-149]. Wider roles for CMV in necrosis of the lung and appendix are discussed in recent reviews [22,29]. During the active infection phase of lung fibroblasts, CMV specifically stimulates cell metabolism resulting in a 5- to 10-fold increase in poliovirus RNAs. In contrast, replication of Vesicular Stomatitis Indiana Virus (VSIV), another RNA virus, was specifically inhibited. Both stimulatory and inhibitory effects were most powerful for co-infection at 48 hours after initial CMV infection, but occur prior to the synthesis of CMV DNA [58]. Ulceration, vasculopathy, and other tissue damage are widely reported in case reports [see 28,56]. Infection in the upper gastrointestinal tract has been shown to lead to both short- and long-term modification of gastrointestinal endothelial, epithelial and stromal cells leading to vasculitis and ulcers, mucosal hyperplasia and polyps, mucosal hypertrophy and thickening along with ulcerated pseudotumors and exophytic pseudotumors [150]. In biliary atresia (BA) patients, perinatal CMV infection appears to initiate bile duct damage aided by a deficiency of regulatory T cells in these patients [151].

In mice, persistent MCMV infection (at a subclinical level) is associated with high blood pressure, where MCMV infection (at single cell level) stimulates expression of rennin [152]. In mice, MCMV infection of the spleen specifically targets endothelial cells of the splenic stroma, inducing significant remodeling of the microarchitecture which results in loss of marginal zone macrophage populations and dissolution of T and B cell compartments [153].

Finally, CMV is now increasingly recognized as an agent for epigenetic modification at the cellular level, leading to altered gene expression [154], and this area has huge potential for disease expression in its own right. The long-term effects of CMV infection in various tissues is far more important than previously thought, and the profound effects of latent infection will now be discussed.

5.2 Sleepless Latency

'Sleepless latency' is the term employed by Pool and Sinclair [155] to describe the expression of cellular miRNAs, intracellular anti-apoptotic and other cellular proteins which occur during latency in primary myeloid cells. One particular protein, LAcmvIL-10, causes a decrease in the cellular miRNA, has-miR-92a, and upregulation of the GATA2 myeloid transcription factor, which in turn drives expression of cellular IL10 [155].

There is now increasing evidence that latent infection with CMV is associated with a wide range of cancers [see section 5.6]. In the CMV genome the UL133-UL138 locus appears involved in a link between latent infection and gastric cancer [80]. Latent infection with CMV (in the presence of EBV) resulting in high levels of CMV IgG is associated with at least two types of cutaneous T-cell lymphoma [79]. In this study 97% to 98% of lymphoma patients were CMV seropositive irrespective of age.

Of central importance to this review is the observation that in healthy volunteers CMV latency-associated proteins elicit immune-suppressive cIL-10 producing CD4+ T cells. These T cells are able to mediate HMC class II restricted cytotoxicity and show IFNγ effector function [67]. CMV therefore has all the tools necessary to both initiate and exacerbate a variety of long-term conditions. It should therefore come as no surprise to note that in the UK those aged over 75+ there is unexplained and high growth in admissions for around 100 diagnoses which are linked with multimorbidity [19,37].

As with mortality, it would appear that the combination of CMV plus inflammatory markers delineates those who are sensitive to the effects of CMV. Hence in patients with coronary disease the combination of CMV plus high CRP was associated with triple-vessel disease, acute myocardial infarction, congestive heart failure, and diabetes [156] – diabetes and CMV being a common theme running through this review.

5.3 CMV and the Efficacy of Vaccination and Immunity

CMV is increasingly recognized as an agent which, cooperatively with ageing, interferes with the efficacy of vaccination (and by implication with wider immunity to other infectious agents) [128,129,157-159]. In one study in Scotland influenza vaccination was 60% effective in those aged less than 65 but only 19% effective in those aged over 65 [160]. How may CMV be involved in this decline in vaccination and immune effectiveness?

In discussing the roles for CMV in vaccination (and immunity) it is important to remember that the effects may be age-dependent. Hence CMV appears to protect teenagers and young adults from respiratory infections [161-162], however the reverse is the case in young children [163-165], and the elderly [22,115,166]. Also recall that only 20% of the population may be highly CMV sensitive and sampling issues may complicate the interpretation of some studies of elderly versus young or CMV positive versus negative. A further complication is the fact the AL18 (an inhibitor of CMV DNA polymerase) is an inhibitor of influenza A and B replication [167], i.e. different measure of success/failure may give conflicting results. Gender-based differences in response to vaccination add additional complexity [168] - see section 5.4 on gender differences.

In one study less than 50% of CMV infected elderly subjects mounted a CD4 T-cell response to influenza antigens whereas around 80% of CMV uninfected individuals did so [169]. Younger individuals did not show this disparity. However, in elderly individuals that did mount a response it was stronger in those who were CMV positive, i.e. the intrinsic difference between CMV-sensitive and CMV-tolerant individuals [169]. CMV has also been shown to affect B-cell response to influenza [128,129,159,166]. In another study, the serum response to influenza vaccine, the number of switched memory B-cells, and the activity of B-cell enzyme AID, were all reduced in both young and elderly subjects who were CMV seropositive. CMV-seropositivity was also associated with higher levels of icTNF-α in B-cells. Serum CMV IgG was also positively correlated with levels of TNF-α [128-129]. This corroborates an earlier study which showed that both young and old influenza vaccine non-responders were characterized by high CMV IgG, increased levels of TNF-α and IL6, higher

proportions of CD57+CD28- lymphocytes, and reduced levels of cortisol. More importantly, influenza vaccination in the non-responders led to an increase in TNF-α and IL-10, i.e. an enhanced inflammatory reaction [170].

How may these factors interact with outbreaks of the proposed infectious agent? Firstly, it is known that deaths and medical admissions during the outbreaks show single year of age specificity suggestive of antigenic original sin [95]. For this reason, all need to be aware that the timing of the study, and previous antigen exposure may have material relevance on the outcome. In its own right the time-based exposure history to influenza A and B is complex [171], as are the corresponding antigen profiles in individuals [172], hence the particular influenza strain will also influence the result depending on the antibody landscape in the subjects. As an example of single measures giving potentially conflicting results, a study conducted in August 2009 in Washington using an Australian produced pH1N1 vaccine, showed that pH1N1 seroconversion following two sequential antibody challenges (21 days apart) was only significantly different in the less than 65 age group between CMV positive and negative subjects. On this occasion pH1N1 seroconversion was measured by haemagglutination inhibition assay [173]. Clearly whatever is happening is more complex than previously anticipated and is occurring across multiple immune domains. However, CMV (latency) is a central element in impaired immunity and vaccine effectiveness. The effect against vaccines other than influenza needs to be investigated.

5.4 Gender Differences

It has been generally observed that female admissions tend to rise more than male admissions during these outbreaks [1-2], and that female deaths from cardio-vascular diseases especially increase relative to males during the outbreaks [31]. Are these observations generally suggestive of the involvement of CMV? The following tend to confirm the association.

Young women are known to be highly susceptible to CMV infection specifically due to unprotected sexual activity [174]. Fig. 5 shows the seroconversion rate for young women in Madrid over the period 1993 to 1999 [175]. Note the large jump in seroconversion rate for those aged 11-15 at the start of the time period who

were aged 17-22 at the end, i.e. from the onset of puberty and potential sexual activity. High seroconversion is maintained through to those aged 21-25 at the start of the time period. Seroconversion drops to very low levels over the age of 30 in these women. Note the low seroconversion among 6-10 year olds who would have been born or been infants at the time of the 1987 outbreak [3].

At age 70, both CMV seropositivity (69% vs 61%) and CMV antibody titre (132 vs 61) were higher in women in the Lothian (Scotland) study [176]. The presence of moderate to high levels of CMV IgG was also noted among female blood donors in Brazil where higher proportions of CMV seropositive occur at a younger age [177]. This higher sensitivity of females to CMV therefore appears consistent with the observed higher sensitivity of females to the outbreaks.

5.5 CMV and the Neurological / Fatigue / Depression / Frailty Paradigm

Fatigue, often associated with depression, effects around 8% of the world population [178]. There appears to be a bidirectional relationship between immune function, depression and sickness behavior (including fatigue) with IL-6 being a key marker [179-181]. Neurological disease sufferers who have chronic fatigue are especially susceptible to a reduction in the number and function of astrocytes, elevated proinflammatory cytokines, oxidative stress and activated Toll-like receptors [182].

During outbreaks of the new disease, it is consistently observed that those suffering from existing neurological disorders, especially Parkinson's, Alzheimer's and dementia, experience the highest increase in deaths [27,32]. Those suffering from neurological disorders are also susceptible to hospitalization from urinary and respiratory tract infections (see Table 4) – conditions known to rise during the outbreaks [1,22]. In England, admissions for those with neurological disorders rose by 32% between 2004/05 and 2009/10 with periods of rapid increase around the time of the 2003 and 2008 outbreaks [25,183]. In the Faroe Islands, the incidence of Multiple Sclerosis has been observed to rise and fall in a series of unidentified infectious outbreaks [184]. A particularly sensitive group of persons appear to have been identified.
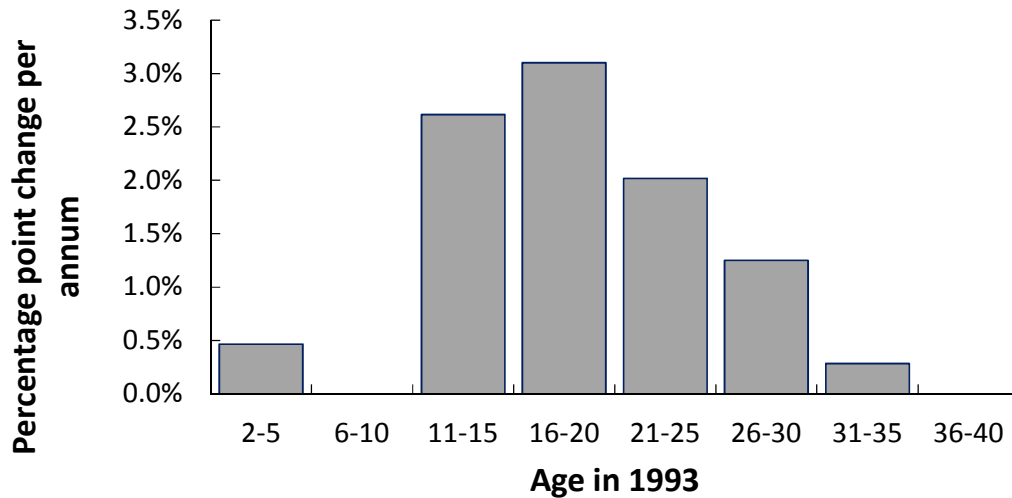
Fig. 5. Change in CMV seroprevalence for women in Madrid between 1993 and 1999
Data of de Ory et al. [175] has been used to calculate the percentage point difference over time for the different age cohorts present in 1993. Seroprevalence in age bands 21-30 and 31-40 has been expanded into four 5-year age bands with values estimated from the original 10-year age bands by interpolation. Age bands are now five years apart while data was collected six years apart allowing sufficient continuity to estimate the change over time. Due to the method of calculation assume that the two age bands (6-10 and 36-40) showing apparent zero seroconversion are actually somewhere less than 0.5% per annum

A key observation to unravelling why those with neurological disorders should be highly susceptible to hospitalization and death during the outbreaks, potentially lies in the fact that 80% to 90% of these patients are subject to chronic fatigue [182], and associated immune disruption. Unsurprisingly CMV is a central player in what can be called the neurological / fatigue / depression / frailty paradigm. This paradigm expresses itself in a manner dependent on age, gender and susceptibility to various conditions [3,6,26,29-30,43]. CMV is also a known psychotropic agent [21]. CMV neuropathies in the *immunocompetent* were a major area of clinical impact observed in the review of Rafalidis et al [56]. Those suffering from psychological stress (anxiety, depression, exhaustion, sleep disturbance and mental health) show stress-related increases in CMV IgG levels [185].

In the brain CMV infects (glia or neurons) of endothelial, tanycytes, radial glia, ependymal cells, microglia and cells from the meninges and chorid [187-188]. CMV is present in 93% of patients with vascular dementia versus 34% in age matched control [189], and raised CMV antibody levels are found in the cerebrospinal fluid of Schizophrenic patients [190]. In another study of the very old, higher CMV IgG was noted to be associated with a higher incidence of Parkinson's (3% versus 1%), although the study

was not large enough to demonstrate statistical significance [73].

Table 4. Common reasons for admission among those with neurological conditions (epilepsy, Parkinson's and multiple sclerosis)

Reason for admission	Frequency
Urinary tract infection	31%
Pneumonia	30%
Lower respiratory tract infection	13%
Syncope	10%
Pneumonitis	8%
Chest Pain (respiratory infection?)	8%
Cataract	7%
Dental caries	5%
Fractured neck of femur	5%
Problems with urinary catheter	4%
Constipation	2%

Data is for residents of the south east coast area of England and covers the years 2009/10 to 2012/13. Adapted from Thomas [186]

In one Alzheimer study, CMV antibody levels were associated with neurofibrillary tangles (NFTs). Cerebrospinal fluid interferon γ was only detected in CMV seropositive subjects and was significantly associated with NFTs. The percentage of senescent T cells (CD4+ or CD8+CD28-CD57+) was significantly higher for CMV-seropositive compared to CMV-seronegative subjects, and was associated with

the pathologic diagnosis of Alzheimer disease (CD4+) or amyloid-β (CD8+). Immuno-cytochemical analysis showed induction of amyloid-β in human foreskin fibroblasts (HFFs) infected with each of 3 clinical CMV strains, HSV-1 infection of HFFs did not induce amyloid-β. In the same subjects, there was no association of herpes simplex virus type 1 (HSV-1) antibody levels with clinical or pathological markers of Alzheimer disease [191]. A more recent study has confirmed a link between CMV infection and the risk of developing Alzheimer's (RR 2.15), and a faster rate of decline in cognitive function. The observed higher incidence of Alzheimer's in blacks was suggested to be due to higher and earlier rates of CMV infection [192].

In older adults depression and anxiety are associated with high CMV IgG levels [193]. In elderly Latinos highest rates of cognitive decline are seen in those with the highest CMV IgG levels [194]. In very old subjects with impaired health and cognitive function, the T cell response to CMV was observed to be more intense, i.e. a proinflammatory response [195].

Fatigue, depression and elevated IgG are commonly observed in those newly diagnosed with breast cancer [196]; and in coronary artery disease, fatigue and depression (along with elevated inflammatory markers) are common in the 12 months *prior* to an acute coronary artery event [197]. The paper of Fagundes et al [196] gives a review of the role of CMV in depression and fatigue. With regard to the issue of CMV sensitive individuals, it has been observed that survival in the oldest old aged 88+ is enhanced in those mounting a pro-inflammatory to CMV compared to those mounting an ant-inflammatory (IL-10) response [198].

In conclusion, in sensitive individuals CMV is central in precipitating a cascade of neurological and immune changes leading to declining mental and physical fitness. Chronic fatigue is both a risk factor and a consequence of CMV infection (in particular individuals).

5.6 CMV and Cancer

CMV is now well-recognized as an oncomodulatory and oncogenic agent [70-87,199-204]. It is possible that the elevated levels of IL-6 produced by infected cells may be the actual cancer promotor [202]. CMV has been associated with cancer when both latent [71,78-80] and reactivated [76,203] and reactivation during cancer therapy [204].

A study of cancer incidence in the USA has suggested that certain CMV-sensitive cancers are diagnosed more frequently around the times of the proposed outbreaks [15]. Data from the whole of the USA is less clear than in other countries due to the sheer size of the country, and the existence of thousands of rural townships. A far higher proportion of the population in the UK live at higher population density than the US [205]. Hence spread of a relatively difficult to transmit agent will lead to undulating time patterns rather than the more observable step-like changes elsewhere [see 1,3,21]. Indeed the ratio of female to male cancer costs in the USA show cyclic behavior around the time of the outbreaks [206]. See section on role of gender.

The authors own unpublished analysis shows that the incidence of breast cancer in the UK changes slightly around the times of the outbreaks, indicating that at least some types of breast cancer respond to the outbreaks. In women newly diagnosed with breast cancer higher CMV IgG levels (but not EBV IgG) were associated with fatigue. While CMV IgG was associated with higher CRP, CRP was not associated with the fatigue [196]. Treatment of glioblastoma with anti-CMV immunotherapy has shown promising results [199]. The linkages between CMV and cancer appear to be wider than first appreciated.

5.7 CMV and Statins

The role of CMV as an agent promoting vascular damage, atherosclerosis and cardiovascular disease is widely recognized [56,117,131-133,207]. It has been recently demonstrated that part of the protective effect of certain statins (atorva-, fluva-, and simva- but not pravastatin) appears to be due to their anti-CMV activity, via the non-sterol isoprenoid arm of the mevalonate pathway. In human aortic endothelial cells, both early and late antigen expression was completely blocked, while the antiviral effects of the statins was comparable to that of ganciclovir, and was retained in a ganciclovir resistant strain of CMV [208]. In those with significant coronary disease (CAD), statin therapy has been observed to significantly lower the risk of death in those who are CMV seropositive (as measured by CMV IgG) and have high CRP levels. Around 46% of CAD patients fell into this high risk group [156].

Given the roles for CMV as an oncomodulatory and oncogenic agent, it is therefore intriguing to note that statins may also play a role in enhancing survival for certain types of cancer including prostate, breast, colon, rectal, epithelial ovarian cancer and other cancers. Statins increased women's survival from common cancers such as breast, bowel and ovarian cancer by 40%. In bone cancer, the death rate was reduced by 55%. Another study showed that men with advanced prostate cancer taking statins were also 40% less likely to die than those who were not [209-213]. We need to ask the question if part of this seeming protective role lies in the anti-CMV properties of statins. None of the above studies seemed aware of this potential link, and CMV IgG levels were not measured. Further work is required to confirm this potential link.

5.8 Disease Time Cascades

Recent studies have indicated that the 'normal' immune and physiological homeostatic states (involving inflammatory / anti-inflammatory balance), which arises from feedback between the immune and endocrine systems (being different between males / females), lies in three equilibrium positions. Illnesses such as Gulf War Syndrome (GWI) and chronic-fatigue syndrome (CFS) establish alternative (and sub-optimal) equilibrium positions [214]. The evidence for one of these sub-optimal positions usually lies in immune activation and cytokine production. This is exactly what has been described in this review for the effects of cytomegalovirus against certain 'sensitive' members of the population. Some 14% of soldiers experienced GWS [214], and CMV studies indicate that around 20% of persons have high CMV IgG (with elevated IL-6 or CRP). This proportion is higher in those with CMV-mediated disease as in CAD, diabetes, etc.

Moving from one equilibrium position to another will take time, as will the expression of diseases arising out of the new equilibrium. It should therefore come as no surprise that outbreaks of the new disease are marked by time cascades for various conditions.

For example, in the 2008 outbreak, GP referral in Wales showed variable increases between the different specialties with mental health and medical referral increasing the most, while orthopedic referral showed a one year lag [12]. Referral to mental health was the only specialty

in Wales showing an increase following the 2010 outbreak [12]. In England, outpatient first attendance following the 2012 outbreak increased in a set of immune-sensitive specialties such as dermatology, nephrology, neurology, rheumatology, and urology; but not in orthopedics, where the immune sensitive conditions would be referred to rheumatology [10], or be subject to a one year lag as seen in Wales. In England, outpatient attendance for various dermatological conditions show different time profiles around the 2008 outbreak [18].

Time-lags have also been observed for various inpatient admissions after the outbreaks. For example, admissions for various allergy conditions displayed two waves after the 2012 outbreak, with some conditions responding immediately and others around 12 months later [26]. There is a lag of around three years for the more aggressive forms of tuberculosis [24], while emergency admissions in oncology show a one year lag – reflecting palliative admission for the terminally ill [20]. Admissions and deaths for neurological conditions appear to rise and fall in an age-dependent manner with the outbreaks [25,27,32].

As a result of these time cascades, admissions for certain age-specialty combinations show higher volatility than others over a time period encompassing five outbreaks [215], as do certain diagnoses in the elderly [216]. In the USA certain types of costs relating to end-of-life also show high volatility over extended time periods [217]. A number studies involving admissions to a single hospital have also demonstrated time cascades for emergency admission for particular conditions [4,5], while in-hospital deaths also show time cascades depending on the condition [30].

An example of the potential role of CMV in such time cascades can be seen in the differential response of early rheumatoid arthritis sufferers to antirheumatic drugs. Those showing a greater inflammatory response to CMV/EBV challenge showed the poorest symptom improvement over a 21 to 24 week period. This poor response was associated with prior CMV IgG but not EBV IgG. Use of methotrexate was associate with up-regulation of the CMV/EBV response leading to poor treatment response [218].

Hence, whatever the primary agent behind these outbreaks, it is highly immune disruptive, and at present CMV remains the closest clinical match.

5.9 CMV Strains and Mixed Infections

There are over 1,400 human pathogens of which there are over 220 viruses [219]. CMV is therefore operating in a context of humans exposed to a range of temporary and persistent pathogens. Table 3 has already demonstrated that mixed CMV/bacterial infections are more likely to result in complications and death. Several reviews have likewise concluded that mixed CMV/viral infections lead to worse outcomes [21-22,28]. For example, CMV and EBV are jointly present in 43% of coronary atherosclerotic tissue [204], and joint infection of endothelial cells by CMV and influenza leads to a 6-fold increase in IL-6 production [220].

Indeed not all CMV strains have similar clinical effects, and some may even prefer different tissue and organ sites to others [see 1,21-23,55]. However, it is clear that mixed strain infections by CMV have worse clinical outcomes due to cooperative effects between CMV strains [see 1,21-23]. Certain CMV UL55 gene variants may be implicated in the development of systemic lupus erythematosus [134]. The proposal that the outbreaks arise from the introduction of a new strain of CMV (or other agent) is therefore feasible given the huge genetic diversity seen in the CMV genome [54,55].

Having outlined the scope for the effects of CMV, is there any evidence that the outbreaks are in fact CMV-related? This question will be explored in the next section.

6. CMV AND THE OUTBREAKS

The authors own unpublished analysis of the number of hospital CMV case reports indicates that cases appear to peak around the years of the proposed outbreaks.

In Australia hospitalization for diagnosed congenital CMV in infants and children between 1993/94 and 200/01 peaked around 1993/94 and 1997/98, which corresponds to outbreaks of the proposed agent [221]. A peak in CMV disease among those with HIV/AIDS was observed between 1995/96 and 1996/97, although in females this was somewhat lengthened to 1995/96 to 1997/98 [222]. These dates also correspond with an outbreak of the proposed agent. In the UK, incidence of CMV infection appears to occur in age cohorts, and measurement between 1991 and 2002 suggested that incidence was highest in those born between 1995 and 1989 [223], and outbreaks of the agent appear to have occurred in the period 1985 to 1987 [121]. CMV infection among neonates in neonatal intensive care units in the USA appears to show a peak around 2009 [224].

Fig. 6 demonstrates how data from existing studies can be re-interpreted in the light of these outbreaks. In Fig. 6 CMV seropositivity is supposed to increase in a roughly linear manner with age, but as can be seen there is a larger than expected proportion who are seropositive for those born in 2006/07, and a far smaller proportion in those born in 2007/08.

While CMV was not measured, in the USA the rate of emergency department visits for elderly patients showed peaks in 1993, 1997 and 2003. Increases were highest in 'other and undefined' diagnoses while the highest increases occurred in those aged over 65, who were black, and required 3 or more medications [226]. All three of these years correspond with dates for the proposed outbreaks [3], and involve those with high risk of CMV active infection [19,21]. Finally, age-specific changes in seroprevalence were noted around the time of the 1993 outbreak in Spain [175]. In this respect mini-epidemics of CMV have also been reported in a variety of contexts [see 21,28].

There are also a number of other studies which overlap the outbreaks. In community dwelling or nursing home residents aged over 50 in Seville (Spain), those who died within a two year period commencing in 2008 (during an outbreak reaching across Europe [2,3]) were characterized by a cytotoxic CD8 CMV pp65-specific T cell response without cytokine or chemokine expression. Those who died had higher percentage of CD107a+PRF1+ CD8 T cells and a higher percentage response by these cells to CMVpp65 antigen [124].

Secondly, in the Norfolk cohort which were recruited between 1993 and 1997 and followed until March 2011, it was found that excluding deaths in the first two years (i.e. during two successive outbreaks in 1993 and 1996) led to a slight reduction in hazard ratios for death [117-118].
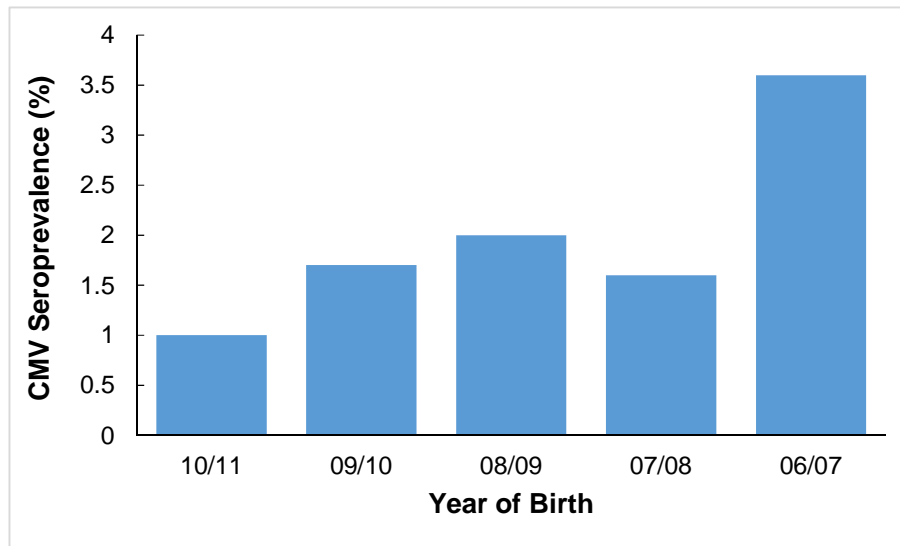
Fig. 6. CMV seroprevalence for children in the USA, by year of birth
Data is from the study of Lanzieri et al. [225]

Finally the question needs to be asked if active CMV infection is more prevalent than has been assumed. In one study of both immune-compromised and immunocompetent subjects CMV was detected in 61% of saliva, 37% of urine and 10% of uterine secretions suggesting that smoldering but subclinical infections are frequent. Detection in the urine appeared to be sensitive to the degree of immune deficiency [227]. In HIV-seropositive women, CMV shedding is specifically related to CD4 T cell levels [228], hence by extrapolation to any other condition leading to a temporary or permanent reduction in CD4 levels. Frequent shedding of CMV in body fluids, especially among children, has been confirmed in a comprehensive review [229], and appears part of the wider susceptibility (by exposure) of women (mothers and nursery school workers) to CMV infection (as discussed in section 5.4).

In conclusion, periods of higher (but age-specific) CMV seroprevalence, admission for CMV related conditions and apparent CMV-related deaths appear to overlap the periods of the new outbreak. Further longitudinal studies are required, especially among those admitted to hospital for medical conditions (especially neurological) or among nursing home residents (the frailty / immunosenescence link). Studies such as the Norfolk cohort [117-118] need to be retrospectively record-linked to hospital admissions to calculate the RR for admissions relating to a wide range of conditions especially in persons with high levels of CMV IgG.

7. CMV VACCINES AND OTHER PROTECTIVE MEASURES

Because of the multiplicity of CMV strains, the development of traditional vaccines has been largely ineffective [230], and more subtle approaches are required [231]. CMV is known to produce IL-10 mimics which are involved in the disruption of CMV immunity. Vaccination of rhesus macaques with engineered non-functional rhcmvIL-10 led to reduced CMV shedding in body fluids [232]. In another trial autologous monocyte-derived dendritic cell vaccines showed no adverse effects against CMV negative volunteers while also inducing a CMV-specific T-cell response. This T-cell response was shown to prevent CMV disease in hematopoietic stem cell transplant recipients [233]. Vaccination during pregnancy with a live attenuated CMV devoid of protein kinase R inhibitory gene resulted in reduced maternal viremia and pregnancy outcomes in the guinea pig [234]. Approaches such as this are likely to lead to successful vaccines in the future.

Curcumin has been shown to provide anti-CMV effects both in vivo and in vitro. In CMV-infected HELF cells curcumin reduced CMV immediate early antigen and UL83A expression, and reduced IL-6 and TNF-α secretion. Cell proliferation was returned to normal levels [235]. Roles for certain statins have been discussed above and statin-based derivatives looks to be a promising route for developing CMV prophylaxis.

8. CONCLUSION

There are hundreds of additional papers which could have been cited in this review. It is hoped that the limited selection has been sufficient to demonstrate that CMV is a far more capable pathogen than previously realized, especially in the presence of a wide range of enabling co-infections and co-morbidities.

This review has also confirmed that the criteria for resolving outbreaks of an infectious disease have been met [236], namely:

a. A pattern in time, place and action
b. Evidence for a shared mode of spread
c. Those affected are among those exposed to the agent
d. Evidence for a unique strain
e. When the source is contained the outbreak wanes

Given the studies showing higher incidence of CMV disease in the years near the outbreaks, the involvement of CMV appears to be highly likely, either as direct pathogen (perhaps via a new strain), or via by-stander activation in the presence of another agent. In its own right the studies on CMV-related mortality confirm that CMV is capable of causing the large percentage increases in death associated with the outbreaks.

Even if CMV is not directly involved in the outbreaks, there is now sufficient evidence to indicate that, in the elderly, CMV should no longer be considered a harmless pathogen, but acts as an unseen force complicating the expression of multi-morbidity and long-term conditions. CMV appears to be a far more insidious pathogen via its sub-clinical effects than via clearly observable clinical CMV disease. CMV is also seemingly acting as a largely unrecognized complicating factor in bacterial infections and conditions such as Alzheimer's, appendicitis, vascular dementia, etc.

Greater emphasis needs to be placed on the observed gender differences in the response to CMV, and on a potential genetic basis for CMV-tolerance. Awareness to hidden infection in various tissues and organs, especially the Islets of Langerhans and the thymus, requires additional studies on tissues extracted during surgery and from cadavers.

The question as to why some 20% of the population appear to be CMV sensitive needs to be the key focus for future research. CMV seropositivity is only of basic interest and can be a misleading indicator, however, CMV plus inflammation (arising from CMV or a multitude of other sources) is an entirely different context.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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