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Chapter 4

Could Cytomegalovirus Be Causing Widespread Outbreaks of Chronic Poor Health?

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Abstract

Evidence is presented for synchronous and recurring increases in medical admissions at between three and eight (most commonly five or six) year intervals. These lead to a typical 10% step-like increase in medical admissions (with other admissions totally unaffected). Such medical admissions are the tip of the iceberg for wider primary care cost increases. A range of non-specific signs and symptoms and specific diagnoses are associated with each step-like increase, whose magnitude increases with age and has a degree of female specificity. Here, the possibility is explored that the ubiquitous herpes virus, cytomegalovirus (CMV), may be behind this international behavior. It is proposed that CMV takes advantage of the wide range of permanent and temporary immune impairments, which exist in what has traditionally been termed 'immune competent' individuals, to exert a wide range of sub-clinical to clinical effects against general population health. Common themes regarding the elderly, signs and symptoms, depression, infection, and inflammation emerge. Indeed, many general practitioner contacts with patients of a vague or syndromic nature may be arising out of the direct and indirect effects of CMV against immune function. Specific research projects needed to test this hypothesis are outlined.

Introduction

The unusually high growth in medical admissions has been an enduring international enigma over the past four to five decades (Hobbs 1995; Kendrick 1995; Capewell 1996;

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Parker *et al.* 1997; Hilder *et al.* 1998; Hilder *et al.* 2000; Morgan *et al.* 1996; Lung and Asthma Information Agency 2001; Kendrick and Conway 2003a-c; NSW Health 2007; MacDonald *et al.* 2008; Roberts *et al.* 2008; Pallin *et al.* 2008; Jones 2009a-i; 2010a-n; 2011a-k; Blunt *et al.* 2010; Gillam 2010). Up to the present, this trend has been largely attributed to factors such as the aging population, health care consumerism, more conservative general practitioners (GP), hospital consultant behavior, and failings in the processes and organization of health and social care. No one seems to have asked the obvious question: could it be that there is a general trend of increasing poor health? Indeed, why have illnesses such as diabetes, allergies, asthma and other immune syndromes apparently increased in parallel with the increase in medical emergency admissions? (Khot *et al.* 1984; Hyams 1998; Anderson *et al.* 2007; Moorman *et al.* 2007; Gonzalez *et al.* 2009; Keil *et al.* 2006).

The author's involvement in this area of research began in 1993 whilst Assistant Director of Information at the Royal Berkshire Hospital (Reading, Berkshire, UK). In the middle of March 1993, the hospital experienced a sudden, unexpected, and permanent increase in medical admissions (Jones 1996a; Jones 1997). Intriguingly, this same event appeared to sweep across the whole of the UK, and a number of studies have sought to explain this behavior (Hobbs 1995; Kendrick 1995; Capewell 1996; Parker *et al.* 1997; Morgan *et al.* 1996). In retrospect, a similar event appeared to occur in New Zealand (Hilder *et al.* 1998). In the USA, an unusual and permanent increase in emergency department attendances also commenced in 1993 (Roberts *et al.* 2008).

My own investigation into this event led to the conclusion that there was some form of infectious outbreak; however, it was not until late 2008 that definitive evidence began to emerge that this was a recurring phenomenon. At this time, I was simultaneously contacted by two large acute hospitals, where managers could not understand why medical beds had suddenly experienced an unexplained influx of patients, and by a Strategic Health Authority seeking to understand why the budgets at Primary Care Organizations (PCO) were suddenly over-spent. Subsequently, I began to search for wider international evidence and explanations in the fields of immunology and virology (Jones 2009a-i; 2010 a-j; 2011a-l).

Since that time, I have also had the unique opportunity of being involved in detailed reviews of emergency medical admissions covering one regional and three PCO geographies in England, and in a review of bed requirements for a large tertiary hospital in Australia (Jones 2011k). All of these reviews were necessitated by the financial and acute bed pressures emanating out of the 2007 outbreak. Most of this work remains unpublished, but only confirms the author's hypothesis regarding an international infectious outbreak. Indeed, when a step change emerges across multiple systems covering a roughly similar set of diagnoses and all clustered around a common initiation date, but with timing differences consistent with something possessing a relatively slow spread (and thereby implying person to person contact), then the possibility of a common infectious cause is highly likely.

The characterization of the unique changes in hospital admission and bed occupancy leading to the analysis of shifts in diagnosis associated with each 'outbreak' was greatly facilitated by the unusually low incidence of influenza over the period January 2000 to August 2009. Such gaps are very rare; the last extended period of very low incidence of influenza occurred between 1879 and 1889 (Thacker 1986). Hence, the analysis of hospital admissions surrounding the 2002 and 2007 outbreaks could be conducted in the absence of the potentially confounding effects of influenza. It is highly likely that the dominating effect

of influenza outbreaks upon emergency admissions prior to 2000 acted to obscure the effects of these 'outbreaks', especially since so many studies use annual totals rather than the daily and monthly time series that the author has used to study the detail of these outbreaks.

In the above context, the re-examination of the long-term trends in medical admissions in the four countries of the UK, USA, Canada and Australia (Jones 1996a; Jones 1997; Jones 2009a-i; 2010a-j; 2011a-k), together with Austria, Estonia and Switzerland (author's unpublished analysis), has revealed curious cyclic patterns, which are reminiscent of the behavior that would characterize an infectious disease outbreak. An excellent example of such cyclic behavior is the observation that the incidence of syphilis (which has an element of acquired immunity) follows an approximate nine year cycle, while that for gonorrhea (no acquired immunity) does not exhibit cyclic behavior (Grassley *et al.* 2005). Every infectious disease involving acquired immunity has its own unique time cycle, which is altered by immunization programmes (Andersen *et al.* 1984; Flemming *et al.* 1991; Dushoff 1996; Dowell 2001; Koelle and Pascual 2004; Grassley and Fraser 2006).

In the UK, the pattern of NHS surplus and deficit, emergency department attendance, bed occupancy, and the size of the inpatient elective waiting list (a knock-on effect from bed occupancy and the availability of funds as a result of the cycle in surplus and deficit) also conform to such a cyclic pattern (Jones 2010f; Jones 2011a,c,h). In the USA, a similar pattern in health care expenditure is known as the 'health insurance underwriting cycle' and leads to a cycle of profit and loss in the health insurance industry (Gabel *et al.* 1991; Kipp. *et al.* 2003; Born and Santerre 2008; Jones 2010c,f).

This chapter will examine the evidence for patterns in acute admissions, bed occupancy and wider health care costs, which cannot be explained by demographic changes, funding, or wider differences in health care organization, policy or implementation. A hypothesis will be explored to investigate if the ubiquitous herpes virus, cytomegalovirus, could be responsible for the range of diagnoses observed that accompany each outbreak.

Upward Trend or a Series of Step-like Changes?

A step change in the rate of admissions or incidence of a disease is an unexpected increase that occurs over a very short time, leading to the establishment of a new, but higher, rate or incidence. This is illustrated in Figure 4.1, using admissions from England over the decade 1998/99 to 2008/09, where two step changes can be seen to occur in the latter part of the financial years 2002/03 and 2007/08, leading to a jump in admissions in the next financial year (April to March). The particular cluster of diagnoses used in Figure 4.1 experience this step change, while other diagnoses follow more usual time trends (Jones 2009i; Jones 2010k-m,i).

This step-like behavior is particular to certain medical specialties (Jones 2009f,i; Jones 2010a,e) and diagnoses (Jones 2009d,i; 2010b,l; 2011c), and is mainly related to emergency or unscheduled admissions (Jones 2009a-e). The unique association of these diagnoses with medical admissions is further illustrated in Figure 4.2. This behavior can be discerned in the four countries of the UK (England, Northern Ireland, Scotland and Wales), Australia, Canada, New Zealand and the USA (Jones 2010f,j-m). Such behavior can also be seen in Austria, Estonia and Switzerland (author's unpublished analysis), and can be inferred from studies

noting an unexplained 10% increase in medical emergency admissions and costs per bed day in Dublin (Ireland) in late 2002, with a specific increase in syncope and chest pain, administration of intravenous antibiotics, and diagnostic ultrasound of heart, abdomen and vessels (Moloney *et al.* 2005). Total admissions in Athens (Greece) also show a step increase in 2002, along with an increase in the variability associated with admissions (Boutsioli 2009). Similar increases in the variation associated with emergency admissions and bed occupancy immediately after each step change have also been noted in the UK and Australia (Jones 2010m; Jones 2011h,m). All the observed step increases appear to initiate around or slightly after the years 2002 or 2007, as seen in Figures 4.1 and 4.2, with evidence for additional step changes in the years prior to 2002 in the USA and UK.

Additional studies have revealed that the step-like changes are also age- and gender-related (Jones 2010f-g,j; Jones 2011c,i), appear to show spatial spread over time (Jones 1996a; Jones 2011a), and involve the totality of health care costs and not just emergency hospital admissions (Jones 2010f,i). The author's own unpublished work suggests that the relationship with age appears to involve some degree of behavior relating to age at the previous 'outbreak', which would be consistent with the phenomenon known as 'antigenic original sin' (Morens *et al.* 2010), where an infectious agent is implicated which invokes an immune response that may or may not be beneficial at the next exposure to this agent. This is consistent with sequential infection by multiple CMV strains (see later).

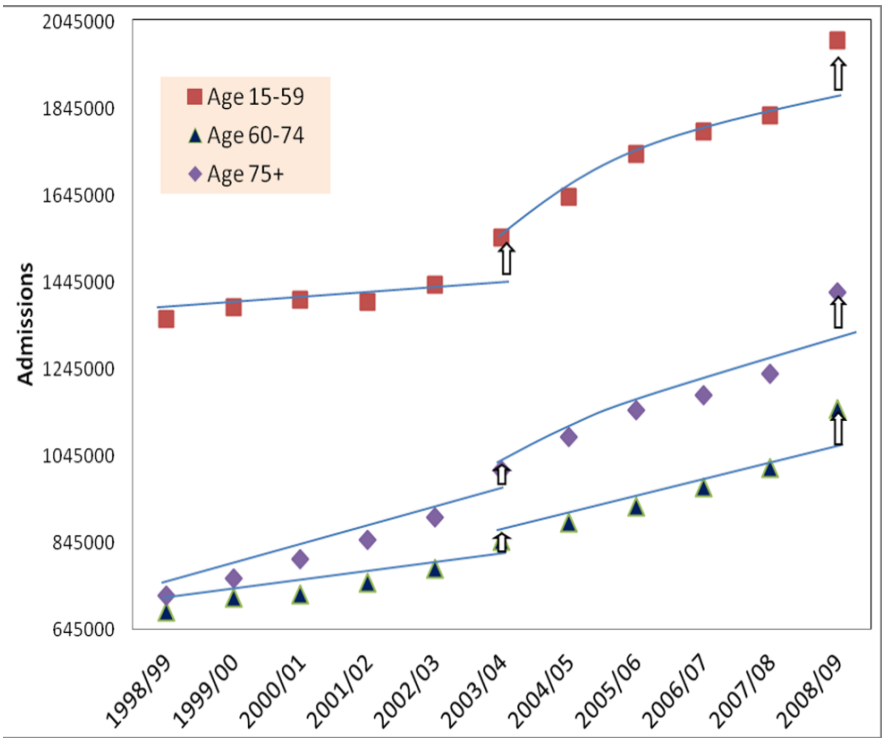

Figure 4.1. Step-like increases in admissions for a cluster of diagnoses across England (Adapted from Jones (2010b) – reproduced with permission from British Journal of Healthcare Management).

Table 1
Pattern in total occupied beds for various regions within England

Strategic Health Authority	2005/06	2006/07	2007/08	2008/09	2009/10	Max: Min
North Central London	95.9	93.1	**79.2**	99.8	103.4	131%
West Midlands South	97.8	98.9	**91.1**	109.7	103.8	120%
North West London	95.1	87.8	**84.9**	100.2	101.9	120%
Bedfordshire & Hertfordshire	97.0	92.8	**88.2**	101.3	103.6	118%
Surrey & Sussex	98.7	92.2	**85.1**	99.4	91.7	117%
Shropshire & Staffordshire	97.3	95.9	**88.5**	99.7	102.1	115%
County Durham & Tees Valley	99.7	106.1	**92.4**	101.9	105.3	115%
Hampshire & Isle of Wight	94.9	87.9	**85.8**	98.4	89.2	115%
North East London	95.7	90.8	**83.5**	92.2	93.6	112%
Northumberland, Tyne & Wear	101.0	96.9	**96.0**	106.3	107.0	111%
Thames Valley	97.6	89.9	**95.1**	95.9	98.8	110%
South East London	96.0	101.8	**93.3**	101.2	98.4	109%
Leicester, Northampton, Rutland	99.1	96.5	**91.7**	94.4	99.9	109%
Birmingham & the Black Country	96.4	94.3	**91.0**	98.9	98.9	109%
Dorset & Somerset	98.8	93.3	**92.6**	100.2	97.1	108%
Trent	98.4	95.6	**93.4**	99.2	101.0	108%
South West London	97.8	92.7	**91.5**	98.1	97.0	107%
Kent & Medway	101.6	97.3	**92.8**	95.1	90.9	107%
Avon, Gloucestershire & Wiltshire	97.6	96.2	**91.5**	97.8	97.6	107%
N & E Yorkshire	97.8	93.4	**89.1**	94.1	94.6	106%
Cumbria & Lancashire	91.2	91.7	**90.5**	95.8	92.0	106%
Essex	101.4	98.3	**94.8**	96.8	100.0	105%
South West Peninsula	96.1	**90.0**	93.3	94.5	93.5	105%
South Yorkshire	101.5	97.7	**94.5**	98.0	99.1	105%
West Yorkshire	97.0	**94.9**	96.0	97.6	93.7	104%
Cheshire & Merseyside	95.3	91.4	**89.1**	92.6	91.4	104%
Greater Manchester	101.6	99.0	**96.8**	97.2	99.8	103%
Norfolk, Suffolk & Cambridgeshire	93.5	86.9	**85.5**	87.7	88.0	103%

Data were extracted from the 'Strategic Health Authority of Residence' tables on the Hospital Episode Statistics (HES) Online website (http://www.hesonline.nhs.uk). Total bed occupancy includes maternity and mental health, and is relative to 2004/05 as the reference point (value = 100.0). Same day stay elective is also included, and has been assigned a nominal one day length of stay to adjust for potential differences in day surgery rates although the effect is minimal. The maximum to minimum ratio is for the maximum bed occupancy occurring after the minimum.

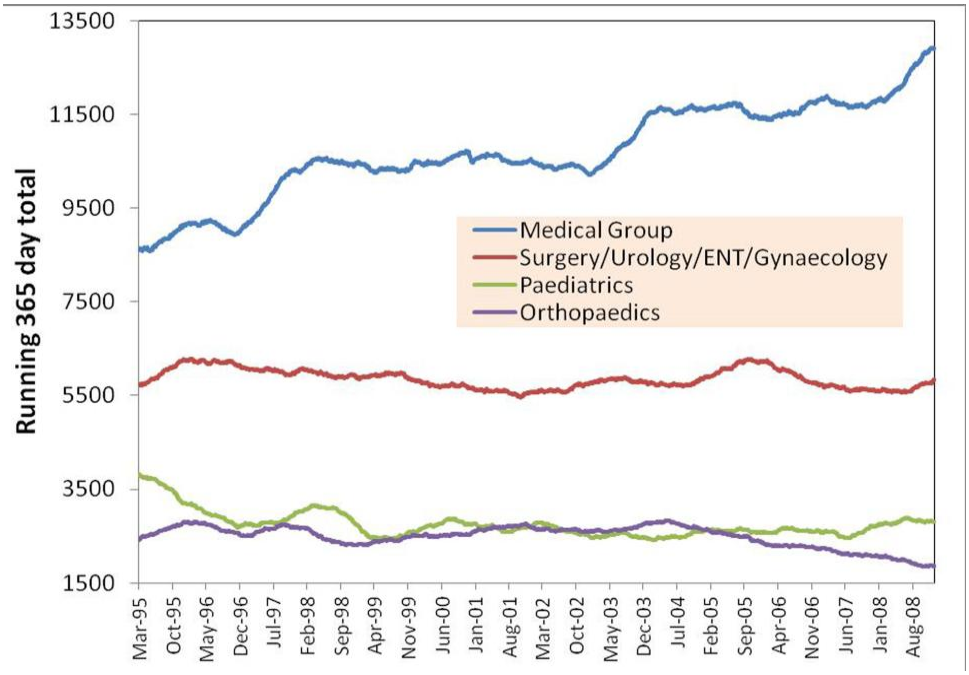

Figure 4.2. Medical and non-medical acute emergency admissions. Data kindly provided by the Royal Berkshire Hospital NHS Foundation Trust. Data exclude zero day stay admissions owing to a potential overlap with emergency department (ED) attendances arising out of the four hour maximum waiting time target. Note that a step change in admission rate will show up as a ramp-like feature in a running 365-day total chart.

Hence, it would seem that large step-like increases in medical admissions and total health care costs are occurring in the major developed countries in a roughly synchronous manner that is suggestive of an infectious outbreak. It would be exceedingly difficult to attribute such changes to any form of common funding, policy, or hospital behavior. A consideration of the diagnoses typically associated with each step change may therefore shed light on the nature of the outbreak or international epidemic; however, before doing this it is useful to investigate the magnitude of the financial and operational implications to international health care.

Financial and Operational Consequences

All health care systems operate within the constraints of financial and operational resources. Throughout the 1980s, the US health insurance industry began to suspect that a cycle of profit and loss may be operating (Kipp *et al.* 2003), and the evidence for this was formally reported in 1991 (Gabel *et al.* 1991). Further research suggested that this cycle appeared to be linked to a curious, sudden, approximately 6% (range 3% to 15%) increase in inflation-adjusted total costs (Born and Santerre 2005; Jones 2010c,f). Such increases will arise from a rapid change in the volume, case-mix and/or complexity of the health care contacts, the sum of which leads to the total cost. The pattern of hospital admissions, occupied bed days and wider costs seen in other countries appears to mirror a cycle very

similar, if not identical, to the health insurance underwriting cycle seen in the USA; although the exact shape of the response over time depends on the geography studied, i.e. for large geographic areas such as the USA the response is a composite of spread over time (as demonstrated in Table 1).

An illustration of the sheer magnitude of such a change is given in Table 1 and Figure 4.3, where the trend in occupied beds within England is examined between 2004/05 and 2009/10. It should be noted that the pattern in occupied bed days is slightly different from that of admissions because the average length of stay is reducing over time (Jones 2009g). This tends to generate a more undulating cycle in occupied bed days rather than the more pronounced step-like pattern in admissions (Jones 2009d,f; Jones 2010a). However, as can be seen, there is a downward trend from 2004/05 either to 2006/07 (four regions) or, most often, to 2007/08, and in just one instance (Greater Manchester), to a minimum covering 2007/08 and 2008/09. The key points are that the downward trend is interrupted by a large (and totally unexplained) increase in the following financial year (although the exact change occurs at a point mid-way through the year), and that considerable regional variation is seen in the spread over time. Neither the downward trend nor the resulting sudden increase can be explained by any demographic, policy, or funding change, and the bulk of the trend is from unscheduled admissions (Jones 2009a,i). Each of the larger districts in Table 1 is made up from around five PCOs, and the pattern observed in these smaller locations is roughly the same, but within the larger regions there is greater evidence for geographic spread over time (Jones 2011a).

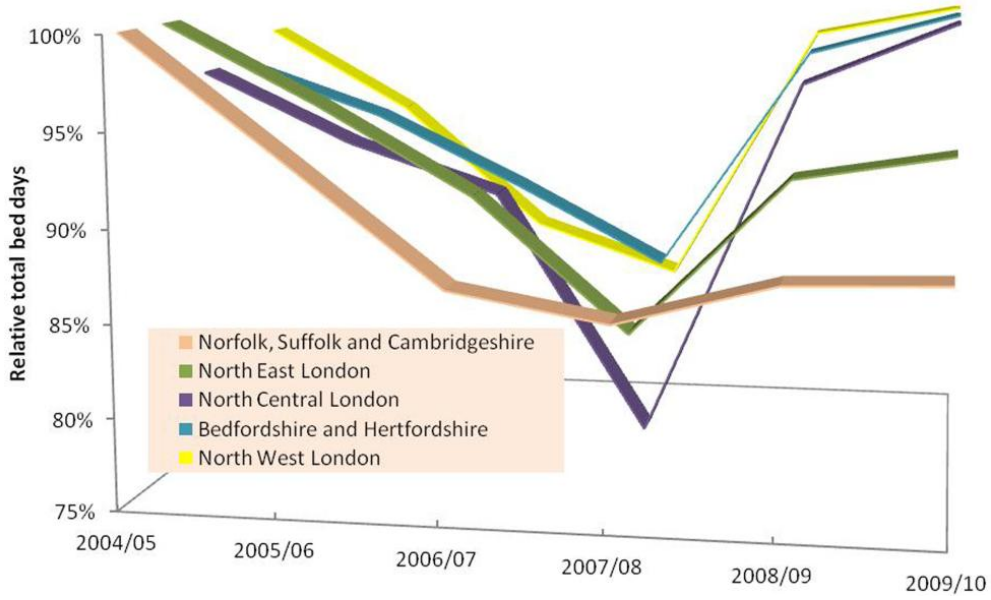

Figure 4.3. Time-based trends for different English regions. Bed demand is relative to the highest year in the time series (value = 100%).

Immediately following this dramatic change, all PCOs across England experienced financial difficulties (Jones 2010a,c,f,i). The varying extent of these financial difficulties can be explained by the different trajectories shown in Table 1, and is further illustrated in Figure 4.3 - North Central London had to cope with a 30% increase in bed-day related costs, while Dorset and Somerset had only to cope with a 7% increase, and Greater Manchester with just a

3% increase. The average increase for England was 7.7%. A 7% step-change in occupied bed-days at a conservative cost of £200 per bed day (Jones 2008) results in a minimum of £680 million ($1,120 million USD) of additional costs, and it is therefore not surprising to note that PCOs in England quickly slid into a deficit similar to that observed in the US health insurance underwriting cycle (Gabel *et al.* 1991; Born and Santerre 2005).

The trend in available beds (as opposed to occupied beds) supports the proposal that the increase in occupied beds was totally unexpected. This then led to the opening of beds that had been previously closed, in order to cope with the additional bed demand (Jones 2009f). While the downward part of the cycle was occurring, the trend showing a reduction in total bed days was widely attributed to 'efficiency' measures acting to reduce the average length of stay, which is partly true (Jones 2009g) but fails to explain the sudden and sustained increase immediately after the minimum point had been reached.

Table 2. List of potential diagnoses which increased after the 2002 and 2007 outbreaks in England

ICD Code	Description	2003/04	2008/09	03/04 step	08/09 step	Category
A01	Typhoid and paratyphoid fevers	247	367	46%	5%	Potential
A03	Shigellosis	68	87	11%	14%	Potential
A07	Other protozoal intestinal diseases	239	212	45%	33%	Potential
A30	Leprosy [Hansen's disease]	21	4	75%	33%	Potential
A38	Scarlet fever	259	421	4%	43%	Potential
A40	Streptococcal septicemia	1,060	1,213	8%	9%	Potential
A43	Nocardiosis	9	8	350%	700%	Potential
A46	Erysipelas	354	281	14%	6%	Potential
A20-A49	**Certain bacterial diseases**			**7%**	**3%**	**Possible**
A50	Congenital syphilis	10	15	43%	88%	Potential
A52	Late syphilis	93	99	29%	8%	Potential
A53	Other and unspecified syphilis	29	26	45%	18%	Potential
A68	Relapsing fevers	6	8	200%	60%	Potential
B05	Measles	108	409	40%	16%	Potential
B09	Viral infection membrane lesions	415	679	11%	19%	Potential
B19	Unspecified viral hepatitis	230	215	28%	10%	Potential
B20	HIV with infectious parasitic	1,040	1,627	8%	11%	Potential
B20-B24	**HIV disease**			**2%**	**4%**	**Possible**
B26	Mumps	143	281	49%	42%	Potential
B33	Other viral diseases, NEC	182	117	60%	19%	Potential
B34	Viral infection of unspecified site	39,911	48,619	4%	12%	Possible
B25-B34	**Other viral diseases**			**4%**	**11%**	**Strong**
B36	Other superficial mycoses	44	65	26%	76%	Potential
B37	Candidiasis	1,489	1,745	11%	3%	Potential
B43	Chromo- & pheomycotic abscess	3	10	200%	150%	Potential

ICD Code	Description	2003/04	2008/09	03/04 step	08/09 step	Category
B35-B49	**Mycoses**			**8%**	**5%**	**Strong**
B56	African trypanosomiasis	9	12	800%	33%	Potential
B76	Hookworm diseases	12	7	71%	250%	Potential
B87	Myiasis	6	15	50%	36%	Potential
B95	Streptococcus and staphylococcus	68	26	10%	136%	Potential
C48	Neoplasm of retro- & peritoneum	1,157	1,526	24%	15%	Strong
D22	Melanocytic naevi	1,464	1,462	15%	22%	Strong
E11	Non-insulin-dependent diabetes	13,669	17,615	7%	8%	Possible
E16	Disorders of pancreatic secretion	7,596	12,900	6%	12%	Possible
E66	Obesity	1,212	5,287	29%	47%	Possible
E87	Electrolyte and acid-base balance	8,521	15,614	19%	15%	Possible
E15-E90	**Endocrine metabolic diseases**			**10%**	**12%**	**Strong**
F10	Mental disorders due to alcohol	31,565	42,995	10%	3%	Possible
F10-F19	**Due to psychoactive substances**			**7%**	**1%**	**Possible**
G00-G09	**CNS inflammations**			**99%**	**107%**	**Strong**
G10-G13	**CNS degenerative diseases**			**96%**	**97%**	**Strong**
G20-G26	**Movement disorders**			**98%**	**105%**	**Strong**
G43	Migraine	6,954	11,282	7%	16%	Strong
G44	Other headache syndromes	2,260	3,178	9%	10%	Possible
G45	Transient ischemic attacks	16,633	21,185	6%	13%	Strong
G40-G47	**Epilepsy, migraine, etc**			**3%**	**23%**	**Strong**
G51	Facial nerve disorders	2,478	3,993	7%	13%	Possible
G97	Postprocedural nervous system	445	797	21%	29%	Strong
H10-H13	**Disorders of conjunctiva**			**9%**	**-**	**Strong**
H35	Other retinal disorders	3,064	4,113	12%	11%	Possible
H47	Disorders of optic [2nd] nerve	448	581	23%	18%	Strong
H53	Visual disturbances	2,641	4,275	11%	16%	Possible
H66	Suppurative otitis media	6,957	6,627	7%	7%	Strong
I00-I09	**Rheumatic heart disease**			**-**	**15%**	**Possible**
I10-I15	**Hypertensive diseases**			**1%**	**10%**	**Possible**
I26-I28	**Pulmonary heart & circulation**			**2%**	**10%**	**Possible**
I34	Nonrheumatic mitral valve	2,553	2,908	10%	6%	Strong
I42	Cardiomyopathy	3,445	3,988	8%	8%	Strong
I48	Atrial fibrillation and flutter	55,910	68,088	6%	2%	Possible
I51	Descriptions of heart disease	1,547	2,331	14%	40%	Strong
I63	Cerebral infarction	35,770	44,354	2%	6%	Strong
I95	Hypotension	8,387	13,635	13%	10%	Possible
I95-I99	**Other circulatory disorders**			**10%**	**9%**	**Strong**
J00	Acute nasopharyngitis	773	1,628	13%	29%	Possible

Table 2. (Continued)

ICD Code	Description	2003/04	2008/09	03/04 step	08/09 step	Category
J00-J06	**Acute upper RT infections**			**114%**	**101%**	**Strong**
J06	Acute upper RT of multiple sites	45,411	50,348	13%	12%	Strong
J10	Influenza identified virus	322	314	201%	140%	Strong
J11	Influenza virus not identified	950	673	42%	28%	Strong
J18	Pneumonia organism unspecified	88,038	125,601	9%	15%	Strong
J10-J18	**Influenza & pneumonia**			**9%**	**15%**	**Strong**
J22	Unspecified acute LRT infection	77,965	91,245	8%	13%	Strong
J20-J22	**Other acute LRT infections**			**8%**	**12%**	**Strong**
J40	Bronchitis not specified	1,265	1,671	14%	11%	Strong
J44	Other chronic OPD	103,917	109,977	13%	10%	Strong
J45	Asthma	55,875	61,048	10%	11%	Strong
J47	Bronchiectasis	5,203	6,430	11%	7%	Possible
J40-J47	**Chronic LRT diseases**			**10%**	**10%**	**Strong**
ICD Code	**Description**	**2003/04**	**2008/09**	**03/04 step**	**08/09 step**	**Category**
J60-J70	**Lung diseases external agents**			**20%**	**5%**	**Strong**
J84	Interstitial pulmonary diseases	4,960	5,854	11%	6%	Strong
J86	Pyothorax	1,910	2,573	11%	11%	Strong
J98	Other respiratory disorders	4,621	5,500	6%	11%	Possible
J80-J99	**Other respiratory diseases**			**4%**	**6%**	**Strong**
K04	Diseases of pulp and periapical	3,974	5,278	8%	5%	Possible
K57	Diverticular disease of intestine	20,702	22,161	3%	3%	Possible
K59	Functional intestinal disorders	34,006	40,602	6%	6%	Strong
K70-K77	**Diseases of liver**			**3%**	**1%**	**Possible**
K85	Acute pancreatitis	13,879	17,160	6%	5%	Possible
K92	Diseases of digestive system	35,839	42,534	3%	6%	Possible
K90-K93	**Other digestive system**			**2%**	**6%**	**Possible**
L02	Cutaneous abscess, furuncle, etc	23,199	28,571	9%	6%	Possible
L03	Cellulitis	48,889	56,232	10%	4%	Possible
L00-L14	**Infections/disorders of skin**			**6%**	**3%**	**Strong**
M15	Polyarthrosis	2,772	7,215	19%	36%	Possible
M25	Other joint disorders	30,681	50,866	6%	21%	Possible
M54	Dorsalgia	33,679	48,031	10%	8%	Strong
M40-M54	**Dorsopathies**			**8%**	**10%**	**Strong**
M62	Other disorders of muscle	2,172	2,520	10%	16%	Strong
M79	Other soft tissue disorders	46,936	66,176	4%	10%	Possible
M60-M79	**Soft tissue disorders**			**6%**	**7%**	**Strong**
N00-N08	**Diseases of the kidney**			**5%**	**8%**	**Strong**
N12	Tubulo-interstitial nephritis	6,405	10,045	11%	14%	Possible

ICD Code	Description	2003/04	2008/09	03/04 step	08/09 step	Category
N17-N19	**Renal failure**			**23%**	**3%**	**Strong**
N20	Calculus of kidney and ureter	21,890	30,502	11%	8%	Possible
N20-N23	**Urolithiasis**			**11%**	**5%**	**Strong**
N25-N29	**Disorders of kidney & ureter**			**3%**	**8%**	**Strong**
N39	Other disorders of urinary system	82,586	130,444	10%	9%	Strong
N30-N39	**Other diseases urinary system**			**7%**	**8%**	**Strong**
N99	Other disorders genitourinary			107%	102%	Strong
O90	Complications of the puerperium	3,961	6,323	16%	5%	Possible
O91	Infections of breast childbirth	509	835	22%	16%	Strong
P08	Disorders gestation & birth weight	5,332	8,827	6%	10%	Strong
P20	Intrauterine hypoxia	23,144	25,084	6%	3%	Possible
P28	Perinatal respiratory conditions	6,612	8,845	8%	9%	Strong
P36	Bacterial sepsis of newborn	1,010	2,310	15%	31%	Strong
P92	Feeding problems of newborn	7,387	12,478	7%	10%	Possible
R00	Abnormalities of heart beat	15,496	21,927	13%	8%	Strong
R06	Abnormalities of breathing	53,006	76,785	8%	14%	Strong
R07	Pain in throat and chest	181,967	252,091	9%	6%	Strong
R00-R09	**Circulatory/respiratory**			**8%**	**7%**	**Strong**
R10	Abdominal and pelvic pain	181,762	227,143	6%	3%	Possible
R18	Ascites	4,854	8,403	13%	9%	Possible
R20	Disturbances of skin sensation	3,621	6,603	10%	17%	Possible
R20-R23	**Skin & subcutaneous tissue**			**2%**	**6%**	**Possible**
R25	Abnormal involuntary movements	2,873	4,125	8%	8%	Possible
R26	Abnormalities of gait and mobility	7,198	6,954	5%	10%	Possible
R25-R29	**Nervous & musculoskeletal**			**5%**	**11%**	**Strong**
R31	Unspecified hematuria	15,736	20,379	6%	6%	Possible
R33	Retention of urine	25,113	27,183	3%	4%	Strong
R41	Cognitive function & awareness	18,341	27,112	12%	13%	Possible
R42	Dizziness and giddiness	12,787	19,252	12%	11%	Strong
R40-R46	**Cognition, perception, etc**			**12%**	**13%**	**Strong**
R47	Speech disturbances,	2,357	5,191	11%	24%	Possible
R50	Fever of unknown origin	15,134	22,455	13%	5%	Strong
R51	Headache	32,540	50,753	9%	9%	Possible
R53	Malaise and fatigue	10,415	14,632	11%	13%	Strong
R54	Senility	27,665	42,175	8%	16%	Possible
R55	Syncope and collapse	64,032	91,643	10%	9%	Strong
R56	Convulsions	35,375	41,528	9%	5%	Strong
R68	Other general symptoms	3,023	5,559	13%	65%	Strong
R50-R68	**General symptoms & signs**			**9%**	**10%**	**Strong**
R69	Unknown causes of morbidity	229,695	116,827	19%	10%	Strong

Table 2. (Continued)

ICD Code	Description	2003/04	2008/09	03/04 step	08/09 step	Category
R79	Abnormal findings of blood	1,710	5,460	25%	15%	Possible
T40	Poisoning by narcotics	6,545	9,954	12%	4%	Possible
T42	Poisoning by antiepileptic, etc	12,608	15,435	11%	5%	Strong
T36-T50	**Poisonings by drugs**			**12%**	**1%**	**Strong**
T66-T78	**Other external causes**			**14%**	**4%**	**Strong**
T83	**Complications GU devices**	**6,825**	**11,279**	**5%**	**13%**	**Possible**
T80-T88	**Surgical & medical care**			**7%**	**5%**	**Strong**
T90-T98	**Sequelae of injuries**			**-**	**25%**	**Possible**
Z04	Examination and observation	10,334	15,273	41%	57%	Strong
Z00-Z13	**Examination and investigation**			**2%**	**14%**	**Strong**
Z27	Immunization	646	333	24%	24%	Possible
Z45	Adjustment of implanted device	6,765	8,467	5%	9%	Possible

Material in this table has been adapted from Jones (2010k,l). The first study used ICD chapter sub-groups, i.e. J02-J22 (Other acute lower respiratory tract infections) in order to gain the benefit of larger numbers (Jones 2010k) while the second study (Jones 2010l) used ICD three digit diagnoses with larger numbers of admissions to investigate in more detail. The 'Category' column gives an assessment of which diagnoses have the strongest evidence for a step change: Strong – good evidence, Possible – possible role for other factors or a knock-on effect, Potential – mainly small number diagnoses.

In conclusion, the financial and operational impact of each outbreak is very large, and leads to significant disruption in the operation of the health care system. How do we go about explaining this cycle of events?

An Infectious Outbreak?

As discussed, the increase in emergency admissions (especially of a medical nature) and emergency department attendances is not a new phenomenon, but goes back at least four decades. However, the point of interest is that this increase occurs at certain points in time rather than as a continuous long-term trend, and that this increase appears to be roughly synchronous among countries.

In this respect, it is well known that all infectious diseases with an acquired immune response exhibit unique time cycles specific to the type of infection (Anderson *et al.* 1984; Flemming *et al.* 1991; Dushoff 1996; Dowell 2001; Koelle and Pascual 2004; Grassly *et al.* 2005; Grassly and Fraser 2005). It has been proposed that the spectrum of diagnoses that commonly increase with each 'outbreak' appear to be associated with some form of immune system disturbance, meaning that admissions for infection and inflammation (in its widest sense) all appear to increase – see Table 2 (Jones 2010k-m).

The evidence that this could be the work of a previously unrecognized infectious agent is as follows (Jones 2006a; Jones 2009a-c,i; Jones 2010k-m; Jones 2011a,d,h):

1. The unique behavior has been consistent over a very long time frame (back to the 1960s).
2. The 'outbreak' results in a step increase specific to medical admissions as opposed to wider surgical, trauma or pediatric, so it is not due to some generalized factor affecting all admissions.
3. Within a very short time (six to eight weeks), the admission rate steps up to a new and higher rate.
4. Regional variability in the timing and extent of the step increase is consistent with an infectious outbreak.
5. The 'outbreak' is characterized by an increase in excess deaths, which lasts for around six to eight weeks.
6. The increase in emergency admissions is accompanied by a permanent and parallel increase in occupied beds.
7. A range of vague and non-specific signs and symptoms plus more specific diagnoses appear to increase during the 'outbreak'.
8. The outbreak appears to coincide with a non-specific increase in GP referral for an outpatient appointment, and this could be interpreted as an increase in general poor health that appears to accompany the outbreak.
9. There is no apparent seasonality, in that similar onsets for each outbreak are observed across northern and southern hemispheres (see later discussion regarding lack of seasonality in CMV reactivation).
10. In the UK there is evidence to suggest that each outbreak initiates earliest in Scotland, and that there is some degree of north to south spread (see later discussion regarding a possible role for vitamin D sufficiency).
11. The author has noted a spatial spread over time among a population admitted to a single hospital by virtue of natural boundaries to movement such as the ocean, rivers or road network, thus a shift in acute thresholds for admission can be ruled out as the cause of this behavior (unpublished analysis).

It is important to note that the increase affecting the greatest number of admissions was for diagnoses of a non-specific nature, i.e. signs and symptoms, and it is the author's opinion that a genuine but subtle step-change in the overall health of the population has occurred. The differential response of the combined acute, primary care and social care system to each outbreak then determines the resulting cost pressures. A poorly integrated system is likely to 'over react', and thereby create additional cost and acute bed pressures. In a poorly integrated system, a large increase in symptoms of poor health, especially among the elderly (where definitive diagnosis is difficult), overwhelms primary and social care and acute admission becomes the default, although it would seem that acute doctors cannot quite explain what exactly is wrong with the additional patients. This additional influx of patients also overwhelms the coding processes within hospitals, leading to an additional increase in default coding (Jones 1996b, Jones 2009h). Factors such as high bed occupancy, leading to hospital acquired infection and allocation of patients into the incorrect specialty bed pool for optimum care (Jones 2009h; Jones 2011f-g,l), act to exacerbate the situation further, and the stretched

resources in health and social care can lead to further blockages to discharge (Jones 2011j). These knock-on effects probably explain the very high increase in occupied beds seen in the health care systems toward the top of Table 1, especially in London (Jones 2011i).

It is postulated that the infectious agent is viral. Certain viruses maintain a state of permanent or persistent infection in the host, and this could account for the step-like change in emergency admission rates, which will arise from the pool of infected persons who could be experiencing some form of impaired or altered immunity. Hence, if the hypothesis of repeating international outbreaks is correct, then we must, of necessity, be looking for a ubiquitous virus known to establish a persistent infection, but that must additionally possess powerful immune-modulating properties. In this respect, the ubiquitous herpes virus, cytomegalovirus (CMV), could be implicated (Jones 2011d), although until recent years this virus has been largely regarded as only posing a risk either to the developing fetus, where it is responsible for 40% of all congenital malformations (Bate *et al.* 2010), or the severely immunocompromised, such as HIV/AIDS and transplant recipients.

Cytomegalovirus

Cytomegalovirus (CMV) is a member of the herpes group of DNA viruses. Varying between countries, 20% to 100% of the population is infected, depending upon the age, gender, region and risk factors (Cannon *et al.* 2010; Hyde *et al.* 2010). It causes a persistent infection with reactivation (via a range of mechanisms) to cause observable clinical symptoms, which include a lupus- or influenza-like illness with fatigue, headache, fever and occasional respiratory infection. These symptoms match some of the more non-specific diagnoses that accompany each outbreak. Indeed, an increase in influenza-like symptoms was noted in primary care during the 1993 outbreak (Jones 1996a). Infection of varying severity can occur in almost any body organ or cell type, and is often resolved with specific anti-viral therapy (Soderberger-Naucler 2006; Varani *et al.* 2009; Varani *et al.* 2010).

Of all the herpes viruses, CMV has the greatest number of genes committed to a formidable arsenal of immune evasive and disruptive strategies directed against the innate and adaptive immune responses of the host (Miller-Kittrell and Sparer 2009; van de Berg *et al.* 2010; Derhovanessian *et al.* 2009), leading to active immune suppression, amplification of inflammation, and autoimmune phenomena (Miller-Kittrell and Sparer 2009; Varani *et al.* 2010; Varani and Landini 2011). CMV also appears to be unique among DNA viruses in that the viron contains four species of mRNA with unknown function (Huang and Johnson 2000).

CMV is curious in that it has no recognized serotypes (in contrast to the influenza virus), but instead has a wide range of strains with high genetic diversity (Stanton *et al.* 2010). Different strains appear to prefer specific organs/tissues, and individuals can be simultaneously or sequentially infected with distinct strains (Ver Braak *et al.* 1998; Stanton *et al.* 2010).

Transmission is via body fluids (blood, breast milk, mucus, saliva, semen, urine and vaginal secretions), and requires a degree of direct contact (Cannon *et al.* 2011). This mode of transmission concurs with the rather slow further spread following the initial outbreak(s). Sexual transmission is one of the more significant risk factors (Robain *et al.* 1998; Cannon *et al.* 2011) The virus can cross the species boundary with primates (Swinkels *et al.* 1984), and

fairly rapid mutation is observed when the virus is subject to serial culture *in vitro* (Stanton *et al.* 2010). Hence, a significant *in vivo* mutation (which is slower than *in vitro*) in a particular strain could be rapidly carried by high volume air, rail, road and sea transport (Hollingsworth *et al.* 2007) from the initial locus to create an international 'epidemic' of poor health. Evidence that CMV seroprevalence is higher in particular years, and the curious gender differences, will be discussed later. It should also be noted that the apparent lack of seasonality with regard to the proposed outbreaks is consistent with direct person to person transmission, and also with the lack of seasonality in CMV re-activation (Ling *et al.* 2003).

Recent research has suggested that a range of sub-clinical effects can also occur, which lead to the virus being a risk factor in a diverse range of clinical situations. These include inflammatory and autoimmune diseases (Varani *et al.* 2009; Varani *et al.* 2010), survival in the intensive care unit (Andre *et al.* 2009), diverse expressions of poor health especially in the elderly (Pawalec *et al.* 2005; Pawalec *et al.* 2009; Vescovini *et al.* 2010; Wang *et al.* 2010), a trigger for breast cancer (Cox *et al.* 2010; Harkinns *et al.* 2010), a trigger for depression (Phillips *et al.* 2008), and as a risk factor in cardiovascular disease (CVD) where CMV seropositive individuals with high C-reactive protein (a marker of inflammation) have a 30% higher risk of death from CVD (Simanek *et al.* 2011). Chronic inflammation in endothelial cells (as in vascular disease) can be induced by the induction of fractalkine when the frequency of CMV-specific T cells is high (Bolovan-Fritts and Spector 2011). Research has shown that CMV is present in 97% of breast ductal carcinoma cases compared to 63% of normal breast glandular epithelium (Harkins *et al.* 2010), and that the elevation of CMV antibodies precedes the development of breast cancer in some women (Cox *et al.* 2010).

A range of studies have shown that the healthy elderly are either not infected with CMV or have very low levels of antibody titer, suggesting that the virus is maintained in a latent state. The frail or unwell elderly are characterized by increasingly high antibody titers (Derhovanessian *et al.* 2010; Vescovini *et al.* 2010; Wang *et al.* 2010), which in one study was linked to associated increases in diabetes, cardiovascular disease, frailty and mortality (Wang *et al.* 2010), and what is known as the immune risk profile (IRP) (Derhovanessian *et al.* 2009; Pawelec *et al.* 2009). The IRP is a cluster of immune changes that appear to mark the onset of the transition ultimately to death. It is characterized by poor T-cell proliferation and response to mitogens, low numbers of B-cells, and an inverted CD4/CD8 ratio caused by the proliferation of CD8 cells and (in most instances) by CMV seropositivity (Pawelec *et al.* 2005; Pawalec *et al.* 2009). CMV also leads to the equivalent of premature aging in T cells, which is linked to diseases such as atherosclerosis (van de Berg *et al.* 2010). Shedding of CMV, which is largely absent in mid-life, is frequently observed in the elderly, along with dual reactivation of both EBV and CMV (Stowe *et al.* 2007). For a large proportion of the elderly the infection has, therefore, switched from latent (or persistent low grade virus replication) to chronic (with active shedding). In this respect the mechanisms distinguishing true latency from persistent, low grade infection are not yet known.

CMV Strain Diversity

As mentioned above, CMV exists as a large and genetically diverse number of strains (Puchhamer-Stockl *et al.* 2011). This is reflected in the glycoprotein diversity of the envelope

(Novak *et al.* 2009), which acts to hamper vaccine development. Multiple strain infections are commonly observed, and up to six strains can simultaneously hyper-infect an individual, with the ratio between these strains changing over time (Gorzer *et al.* 2010). Some 16% of congenitally infected infants have multiple strains (Ross *et al.* 2010), and in a study of healthy young women who had only recently become seropositive to CMV, some 25% had an identical strain, 71% harbored unique strains, and 4% had two strains (Murthy *et al.* 2011). In another study, multiple clusters of strains were detected among children at six day care centers in two cities in the USA (Bale *et al.* 1999). Since CMV is uniquely characterized by such an enormous variety of strains, why is such diversity needed? It is proposed that strain diversity is the unique answer to optimum infection in humans exhibiting a similarly diverse range of immune impairments. Such differences may also enable each strain to exhibit a degree of organ specificity (Woo *et al.* 1997). It is proposed that descriptions such as 'immune competent' or 'healthy' have failed to indicate the correct situation, and that the issue of immune impairment needs to be more widely appreciated.

Immune Competent?

The classic textbook description of CMV infection is that it is largely dormant and without observable clinical symptoms in most immune competent hosts, and that only the immune compromised host is at risk of serious clinical infection. However, such a clear cut distinction may have acted to deflect clinical and research interest away from the more subtle effects of this virus.

Indeed, to understand the maximum potential for this virus to act, we need to understand the much wider range of permanent and temporary immune impairments that characterize the supposedly 'immune competent' or 'healthy' host. All individuals have the potential for some degree of temporary or permanent immune impairment due to a wide variety of factors such as: ageing (Lustgarten 2009; Mayor 2009; Deeks and Phillips 2010), gender, especially around puberty (Tanriverdi *et al.* 2003; Fairweather and Rose 2004; Jaspan *et al.* 2006; Lamason *et al.* 2006; Libert *et al.* 2010), the developing fetus and very young children (West 2002; Tu *et al.* 2004), pregnancy (Jamieson *et al.* 2006; Westman 2010; Kastelan *et al.* 2010), circadian cycles in immune components and sleep disruption (Born *et al.* 1997), strenuous physical activity (Gleeson *et al.* 2004), chronic stress and anxiety (Kiecolt-Glaser *et al.* 1987; Kiecolt-Glasser and Glasser 2002; Prasch *et al.* 2000; Davidson *et al.* 2003; Reiche *et al.* 2004), war, natural disasters and trauma (Hyams *et al.* 1996; Ironson *et al.* 1997; Vojdani and Thrasher 2004; Whistler *et al.* 2009), depression (Kiecolt-Glaser and Glaser 2002; Dantzer *et al.* 2008), exposure to environmental toxins, including the resulting DNA damage (Hyams 1998; Kawanishi *et al.* 2006; Ohshima and Bartsch H 1994), poor nutrition (Linder 1987; Azad *et al.* 1999; Savino 2002; Gleeson *et al.* 2004; Evans 2005; Haase and Rink 2009), deficiency in iron, zinc and selenium (Broome *et al.* 2004; Hurwitz *et al.* 2007; Wardwell *et al.* 2008; Mocchegiani *et al.* 2009; Haase and Rink 2009; Papp *et al.* 2010), acid/base imbalance (Lardner 2001), season of the year, altitude and latitude, including magnitude of exposure to ultraviolet radiation and vitamin D levels (Dowel 2001; van der Mei *et al.* 2001; Altizer *et al.* 2006; DeLappe *et al.* 2006; Grassley and Fraser 2006; Zittermann *et al.* 2009; Hayes 2010), existing autoimmune disease(s) (Gottleib *et al.* 1979), variation in thymic T-cell

production (Lorenzi *et al.* 2008; Lorenzi *et al.* 2009), genetic factors, including specific gene mutations (leading to what are known as primary immunodeficiencies) and epigenetic factors such as environment-induced DNA methylation (Casanova *et al.* 2008; Thomas *et al.* 2009; Hamza *et al.* 2010; Bousfiha *et al.* 2010; Mathers *et al.* 2010), which may explain the unique patterns in immune response that render some individuals resistant to HIV infection (Suy *et al.* 2007), type 1 or type 2 diabetes (Muller *et al.* 2005; Danquah *et al.* 2010), diseases such as cirrhosis of the liver (Varani *et al.* 2000), or the presence of persistent viral infection (Bonhoeffer and Nowak 1994; Worobey and Holmes 1999; Goulding *et al.* 2001; Wills *et al.* 2002; Wherry *et al.* 2003; Garcia-Pineres *et al.* 2006; Freeman *et al.* 2006; De Martel *et al.* 2008; Voisset *et al.* 2008; Zuniga *et al.* 2008; Deeks and Phillips 2010).

Given the complexity of the immune system, and the fact that new classes of immune cells are regularly being discovered (Miossec *et al.* 2009), such observations are not surprising and suggest that the supposedly 'immune competent' population has a wide variety of exploitable immune impairments. If we accept the proposal that the multiplicity of CMV strains is central to the biological success of this virus, we then have a basis for understanding how the seemingly immunocompetent population could experience a wide range of sub-acute, acute and chronic CMV infections. Indeed, the whole issue of immune impairments may be central to the explanation of *in vivo* CMV biology, and the very use of averages and tests for statistical significance are based on the assumption that individuals react to infection and disease in a unique way.

We now need to reconcile the observed characteristics of the outbreaks of poor health against the known and potential effects of CMV, and the following sections will investigate several of the key areas.

The Elderly

In England, 50% of all admissions (including elective/planned) are for those aged over 60, and this proportion reaches 65% for the medical group of specialties. In the elderly, infection often manifests as changes in cognitive function (including depression) and physical function, rather than the classical signs of infection seen in the young (High *et al.* 2005). Chronic inflammatory conditions associated with high levels of circulating cytokines lead to muscle wastage and disability (irrespective of age), although in the elderly the natural innate inflammatory responses are enhanced and prolonged (High *et al.* 2005, Stout-Delgado *et al.* 2009). Assessment scores for both cognitive and physical function are therefore good predictors of emergency department attendance (Walker *et al.* 2005) as well as infection and/or inflammation, and can often continue to decline after the immediately apparent cause of the 'infection' (urinary tract infection, pneumonia, etc) has been treated (High *et al.* 2005). In elderly Latinos, functional impairment has been shown to be clearly linked to levels of C-reactive protein (CRP), which is a marker for inflammation, and CMV has also been implicated (Aiello *et al.* 2008a). The role of CMV inflammation is discussed in more detail in a later section.

Several studies have noted that specific and unexplained increase in admissions, as described in Chapter R of the International Classification of Disease (ICD) 'signs and symptoms', is associated with an increase in medical emergency admissions for the elderly

(Walsh *et al.* 2008, Kendrick and Conway 2003a-c, NHS Scotland, 2005), especially R00-09 (circulatory and respiratory) and R50-68 (general signs and symptoms) (Blunt *et al.* 2010). Re-analysis of the same data has demonstrated that particular signs and symptoms exhibited a characteristic step-like increase immediately after the 2002 and 2007 'outbreaks' seen in the UK (Jones 2009i; Jones 2010k-m) and a similar 'outbreak' seen in Australia (Jones 2011k). In the USA, a specific increase in emergency department attendances for 'other and undefined diagnoses' has been observed since 1993, and this translated into peaks in admission via the emergency department around 1993, 1997 and 2003. The highest increase was noted in those aged over 65, of African descent, and requiring three or more medications (Roberts *et al.* 2008). Hence, the general difficulty in assigning a definitive diagnosis in the elderly is consistent with the specific step increase in admissions for signs and symptoms, and this may have masked the true underlying etiology.

In addition to the more general 'signs and symptoms', there is an additional set of more specific diagnoses that appear to be implicated, and these are listed in Table 2. While the list in Table 2 may appear somewhat extended, it should be noted that it represents a very small subset of the 1,655 ICD diagnoses used across England (of which the top 200 account for 75% of all admissions). However, in its widest sense all diagnoses have a common link with infection or inflammation, with the inflammatory immune responses and the consequences of these.

Additional research into this list is required, as some have a 'confirmed' step increase while others are possible diagnoses requiring further validation. Indeed, it is possible that some are direct effects of the outbreak while others are indirect or knock-on effects. Diagnoses relating to cancers, neonates and congenital conditions are largely unstudied. It is also possible that some of the diagnoses noted in Table 2 may be 'nearest fit' diagnoses. The issue regarding the accuracy of diagnosis is discussed later. If we accept that we are dealing with a relatively slow moving infectious outbreak leading to a cascade of diagnoses, some of which may involve time lags, then complex spatial analysis is required to match up the point of onset in each location to magnify the resulting diagnostic changes over time. This approach will then allow greater clarity as to which diagnoses are genuinely associated with the outbreak, and the degree of time lag for other diagnoses that may also be gender related (Jones 2011c).

Gender

While the two genders appear to have identical immune systems, evidence is emerging for gender-specific immune functional differences. Each autoimmune disease exhibits a unique gender ratio regarding incidence (Libert *et al.* 2010), and only women are capable of the unique immune changes required during pregnancy (Westman 2010). One of the characteristics of the curious step-increase in medical admissions is an apparently greater effect against females, or gender- and time-related effects in particular diagnoses (Jones 2009i; Jones 2010f,g,j; Jones 2011c,i). In this respect, CMV seropositivity is more prevalent in females and generally occurs at an earlier age (Matos *et al.* 2010), and this has been attributed to greater exposure to young children who can shed CMV for up to 29 months post infection (Tu *et al.* 2004). CMV antibody levels are usually higher in women (Matos *et al.*

2010), and women show a higher release of interferon-γ and interleukin-2 than men in response to active CMV infection (Villacres *et al.* 2004).

Role of the Thymus

The correct function of the thymus in attracting and converting bone marrow-derived precursor cells is vital for the production of T lymphocytes (see review by Boyd *et al.* 2008) and dis-regulation of this process leads to autoimmunity (Baldwin *et al.* 2004). CMV is now strongly implicated in a range of autoimmune diseases (Varani *et al.* 2009; Varani *et al.* 2010; Varani and Landini 2011). Measles, HIV, varicella-zoster, coxsackievirus-B4, echovirus type 6 and CMV are all capable of infecting the thymus (Numazaki *et al.* 1989; Valsamakis *et al.* 1998; Ventura *et al.* 2001; de la Rossa and Leal 2003), leading to various impairments in T-cell production, the production of virus-infected T-cells (such as with HIV), and reduced secretion of interleukin-1-like activity (Wainberg *et al.* 1988; King *et al.* 1992; Brilot *et al.* 2004). The thymus is also a specific target in malnutrition (Linder 1987; Savino 2002), suggesting that the malnourished elderly, who are over-represented in acute medical admissions (Azad *et al.* 1999; Evans 2005; Haase and Rink 2009), could be a specific target for CMV. In some instances the virus can be eliminated from the thymus by the addition of donor T-cells containing virus-specific cytotoxic T lymphocytes (King *et al.* 1992), and this may explain the beneficial effects of thymus extracts in treating instances of chronic respiratory tract and other infections (Wilson 1999).

The production of T-cells by the thymus can be accurately determined using T cell receptor excision circle (TREC) studies. TRECs are episomal DNA by-products of T cell receptor rearrangements that are only expressed by T cells of thymic origin, with each cell containing a single copy of TREC. In 'healthy' individuals the TREC count declines in a logarithmic manner with age, from around 1.1 x 10^9 cells per day at age 1 to around 1 x 10^7 at age 80, and this is also associated with a change in the ratio of CD4+/CD8+ and CD8_TREC/CD8+ (Ye and Kirschener 2002; McFarland *et al.* 2000). However, for individuals of the same age, thymic T-cell production can vary by at least 10-fold, with the extent of this variation appearing to be least between 15 and 35 years, then significantly increasing above age 35 (Lorenzi *et al.* 2008). Production of T-cells is typically higher in females (Lorenzi *et al.* 2008; Lorenzi *et al.* 2009). Aberrations in thymic morphology and reduced T-cell production are known to be associated with auto-immune, infectious, and allergic diseases (Zairat'iants 1991) such as myasthenia gravis (Vakilian *et al.* 2006), systemic lupus erythematosus (Gottlieb *et al.* 1979; Kayser *et al.* 2004), rheumatic heart disease (Henry 1968) and inflammatory skin diseases such as atopic dermatitis (AD) and psoriasis (Just 2006). Interestingly, patients with AD exhibit a high variation in TREC over time (Just 2006), which appears to be a similar phenomenon to the symptom flare cycles observed with Lyme disease, and may arise from oscillatory cycles in cytokine levels triggering an autoimmune response (Gruber 2010).

The vital role of the thymus in maintaining immune function following CMV infection has been demonstrated in a study investigating patients whose thymus was removed during early childhood. In this study, CMV-infected thymectomized patients who had reached the age of 22 exhibited an altered T cell profile characteristic of those aged over 75, which was

similar to the IRP. The strongest alteration in this profile was associated with a group of patients who were 86% CMV seropositive, in contrast to other thymectomized patients who were only 36% CMV seropositive (Sauce *et al.* 2009). In AIDS, it has also been noted that restoration of thymic mass by growth hormones acts to restore T cell production (Taub *et al.* 2010).

In one study using human thymic tissue grafted into SCID-hu mice, human CMV (HCMV) was concentrated in the medulla of the thymus, with the epithelial cells being the primary target rather than the hematopoietic cell population (Mocarski *et al.* 1993). Similar damage to the thymic epithelial cells occurs in severe malnutrition due to expansion of cytotoxic suppressor (CD8) lymphocytes, which has been proposed to lead to immune dysfunction (Linder 1987). In guinea pigs with CMV-induced mononucleosis, the virus was cleared from the blood and bone marrow within one month; however, it remained resident in thymic and lymph tissue (Griffith *et al.* 1981) with unknown long-term effects. In BALB/c mice infected with a sublethal dose of murine CMV (MCMV), the thymocytes exhibited extensive apoptosis due to aberrant Ca^{2+} mobilization, although MCMV DNA could only be found in the thymic stromal cells and not in the thymocytes (Koga *et al.* 1994). It is clear that CMV can establish long-term infection in the thymus, leading to the production of defective (but not infected) thymocytes. Such resident CMV infection could also hasten the decline in thymic function with age, as evident by the wide range in TREC production observed in humans of the same age (Gress and Deeks 2009). Lastly, in patients with hematological malignancies, naïve CD8 cells from umbilical blood failed to clear CMV viremia, but required T cell neogenesis (as $CD4^+CD45RA^+$) via the thymus to be effective (Braun *et al.* 2010). It is widely recognized that, in some individuals, up to 30% of the circulating $CD4^+$ and $CD8^+$ memory cell population is committed to controlling CMV (Sylwester *et al.* 2005, Naeger *et al.* 2010), and this compromises the patient's ability to respond to new infections, thus leading to the observed increase in susceptibility to infection during each outbreak. Under these circumstances it is only those individuals with an active thymus who will have the reserve capacity to continue producing non-CMV committed T-cells.

There appear to be no studies regarding the possible role of CMV infection of the thymus in the progression of immunosenescence, various system diseases, or premature death. In this respect, testing for CMV infection during autopsies of those dying from different diseases or at different ages may shed further light on this topic.

Vitamin D

In the UK each outbreak appears to commence slightly earlier in Scotland, and shows some degree of north-south movement (Jones 1996a; Jones 2010i). It has been suggested that vitamin D sufficiency/insufficiency may explain this observation (Jones 2010i). Vitamin D is known to be involved in both innate and adaptive immunity, and hence, autoimmune disease, various diseases including some cancers, resistance to infection, the production of antimicrobial peptides called defensins, and depression (Adams and Hewison 2008; Yamschchikov *et al.* 2009; Zitterman *et al.* 2009; Ganji *et al.* 2010; Sabetta *et al.* 2010).

It is of interest to note that 1,25 $(OH)_2$-vitamin D3 is concentrated in the nuclei of reticular cells of the medulla and cortex of the thymus (Stumpf and O'Brien 1987), but not in

the nuclei of lymphocytes. However, vitamin D receptor (VDR), a member of the nuclear receptor family of transcription factors, is found in significant concentrations in the immature cells of the thymus and in mature CD8 T lymphocytes (Deluca and Cantorna 2001). Hence, vitamin D levels could also play an important part in regulating thymic function (discussed above), along with wider infection/inflammation issues.

There is only one study to date regarding vitamin D levels and CMV, dealing with pediatric onset multiple sclerosis (MS). The MS group, rather surprisingly, had lower CMV antibody levels associated with vitamin D insufficiency and, conversely, vitamin D sufficiency was associated with higher CMV antibody levels, while in the control group, vitamin D sufficiency was associated with lower CMV antibody levels (Mowry *et al.* 2011). It would appear that, in the absence of MS, vitamin D sufficiency is implicated in avoiding the deleterious effects of CMV, with low CMV antibody levels suggesting controlled infection, but may interact with particular immune impairments in unexpected ways. See the next section for a similar dichotomous response to CMV inflammation in the presence of a specific gene mutation.

More research regarding the role of vitamin D sufficiency/insufficiency in association with CMV infection is required, especially for the elderly where diminishing renal function leads to hyperthyroidism, requiring a higher intake of vitamin D to counteract this effect (Vieth *et al.* 2003), and in pregnancy where vitamin D deficiency is implicated in impaired maternal and fetal outcomes (Lapillonne, 2010) – could this be a hidden interaction with CMV infection?

Inflammation

The observed cluster of inflammation-related diagnoses is an important clinical benchmark, and CMV-seropositive individuals with elevated CRP have a 30% increase in all-cause mortality (Simanek *et al.* 2011), indicating wide-reaching effects promoting disease in its widest sense. This has been termed mosaic aging, where the weakest organ/system fails first (Walker and Herndon 2010), and CMV may be the 'stress factor' in particular cases.

In elderly Latinos, functional impairment has been shown to be clearly linked to levels of C-reactive protein (CRP), which is a marker for inflammation, in which CMV was also implicated (Aiello *et al.* 2008a). However, the linkage with CMV becomes clearer when it is realized that the APOE-epsilon 4 genotype leads to alternative CRP responses (Aiello *et al.* 2008b). Those possessing this particular genotype have lower levels of CRP and exhibit higher levels of CMV antibodies. This disparity in the role of CRP explains why the role of CMV was difficult to discern in the study using just CRP levels as an inflammatory marker (Aiello *et al.* 2008a), as specific immune impairments lead to particular pathways of CMV attack. The APOE-epsilon 4 genotype response was noted to be specific to CMV, not to HSV-1 (Aiello *et al.* 2008b).

Dendritic cells (DC) are highly specialized cells that determine the quality and magnitude of immune reactions against foreign- or self-antigens, and exposure to exogenous or endogenous interleukin-10 (IL-10), an anti-inflammatory cytokine, is critical to their maturation, effectiveness and longevity (Chang *et al.* 2007). CMV contains genetic material encoding a specific IL-10 homolog (an IL-10 impostor), which is highly effective at

inhibiting the maturation and functionality of DC at all stages of DC activation (Chang *et al.* 2004), and also suppresses type 1 interferon production by DC (Chang *et al.* 2009). These two factors initiate a cascade of long-term deficits in both innate and adaptive immune and inflammatory responses (Slobedman *et al.* 2009, Chang and Barry 2010), which can be used to explain why both active and apparently 'inactive' CMV infection can lead to increased sensitivity to infection and inflammation. During productive infection, CMV is also known to produce at least five other less abundant IL-10 like variants (Slobedman *et al.* 2009).

In addition to the above, CMV infection increases the expression of 5-lipoxygenase (leading to leukotriene B4 production) and COX 2 (and therefore prostaglandin release), which are crucial in inflammation (Qiu *et al.* 2008), along with other inflammatory cascades (Varani and Landini 2011). Lymphocytes in the elderly are known to be more sensitive to the inhibitory effects of prostaglandin E2 (Goodwin 1979).

Hence, it would seem that specific mechanisms do indeed exist for CMV to initiate an increased susceptibility to infection and an increase in inflammatory-related conditions, as observed in the outbreaks of acute hospital admissions.

Chronic Disease

There are several additional intriguing possibilities for the role of CMV in chronic diseases. The first comes from the observation that the expression of CMV genes in infected cells leads to mutations in the host DNA, acting to sensitize the host DNA to mutagenic agents (Albrecht *et al.* 1997). It is possible that one of the adverse roles of CMV in the developing fetus is to cause gene mutation (Cheeran *et al.* 2009). The second possibility comes from the encyclopedic study of Hanan Polanski (2003) into the role of micro-competition between foreign DNA and host DNA in the regulation of gene expression. Microcompetition in effect leads to gene expression, which acts as if the gene were mutated, and this then leads to the initiation of a variety of chronic disease processes. This mechanism is especially relevant to the range of cell types (such as microglia) where CMV enters the cell, releases its DNA, but does not progress to productive infection (Cheeran *et al.* 2009).

Lastly, poor psychological well-being and chronic heart failure have both been observed to be associated with shorter leukocyte telomere length (Huzen *et al.* 2010), and the same effect on both leukocytes (differentiated T-cells) and lymphocytes has been noted in active CMV infection (van de Berg *et al.* 2010). Shortened telomere length in circulating leukocytes has been proposed to be associated with age-related diseases such as atherosclerosis (Huzen *et al.* 2010). All of the above are plausible but largely unstudied areas for potential roles for CMV in the accelerated aging of the immune system and disruption of DNA expression, leading to chronic disease.

Under-Diagnosis in the Primary Care

In general practice, fewer than 20% of the most frequent diagnoses account for 80% of consultations, hence, just 20% of consultations relate to the 80% of less frequent diagnoses. In general, 50% of diagnoses remain a description of symptoms, 40% are named syndromes,

and only 10% are confirmed diagnoses (Fink *et al.* 2009). Since CMV is only considered to be a danger to the developing fetus (Revello and Gerna 2002) and in the seriously immunocompromised (Boeckh and Geballe 2011), the majority of GPs will not even consider CMV as a possibility behind non-specific symptoms. However, although it is thought largely to lie latent, CMV can be isolated from 61% of saliva samples, 37% of urine samples and 10% of uterine secretions, suggesting that 'sub-clinical' active infection is fairly frequent (Gautheret *et al.* 1997), and one of the key observations of a recent review is that "seroconverting adults shed for many months rather than weeks" (Cannon *et al.* 2011). Of particular interest is the fact that detection in urine depends on the degree of immune deficiency; it is more common in those with HIV (Gautheret *et al.* 1997) and is specifically related to the level of CD4 cells (Clarke *et al.* 1993). In this respect, it is of interest to note that the review of Cannon *et al.* (2011) on CMV shedding appears to show that in children there is a disposition to shedding in the urine compared to saliva, and this might be linked to the observation that children appear to have a specific CD4-based immune weakness specific to CMV (Tu *et al.* 2004). The comments above regarding the range of immune impairments are apposite, and the ratio of saliva/urine positive samples may well prove to be an indicator of particular types of CMV-specific immune impairments.

Especially relevant to the primary care context is the association between active CMV infection and depression (Phillips *et al.* 2008), an effect that is also common in other immune impairing diseases such as HIV infection (Evans *et al.* 2002), Lyme disease (Rissenberg and Chambers 1998) and hepatitis C infection (Goulding *et al.* 2001). It is of interest to note that primary care costs associated with markers of depression and mental health increased by over 20% following the 2007 outbreak in England (substance misuse +31%, organic mental disorders + 24%, psychotic disorders +43%, chronic pain +20%, poisoning +39%) (Jones 2010i). The links between inflammation and depression are being increasingly recognized (Dantzer *et al.* 2008), but could these be the tip of the iceberg for primary care?

Studies investigating the prevalence of high levels of CMV antibodies are likewise needed in a primary care setting, especially for patients exhibiting unexplained physical and apparent psychological/neurological symptoms. For example, young mothers who have just become CMV seropositive via contact with their own children show prolonged CMV shedding for up to six months, but in some individuals this can last up to 15 months (Tu *et al.* 2004). Do these represent a particular risk group for secondary infections and depression? Out of interest, the author asked a GP for a list of common consultations regarding health issues in young mothers, and the following were identified: menstrual pains, headache, abdominal bloating, depression and tiredness (Dr Clare Gerada, personal communication). These are non-specific syndromes, which will require further investigation to see if they correlate with active CMV infection, especially since sleep disruption is common in young mothers and is a known cause of immune impairment (Born *et al.* 1997). Indeed, a wider study investigating levels of CMV antibodies (or CMV seropositivity plus indicators of inflammation and/or low grade infection) in patients consulting their GP regarding symptoms of tiredness and lethargy is probably needed.

Under-diagnosis in Hospital Care

In recent times, clinicians have increasingly recognized a variety of CMV-induced diseases (or disease mimicry) in 'immunocompetent' patients, which resolve with anti-viral treatment (Varani *et al.* 2000; Varani *et al.* 2009; Varani *et al.* 2010; Varani and Landini, 2011). For example, one previously healthy young patient developed life-threatening fulminant pneumonia due to co-infection with *Mycoplasma pneumoniae* (Jacobi *et al.* 2010). Given that the lung is a major organ for CMV infection, it is not surprising to note that interstitial pneumonia is a frequent manifestation of CMV re-activation or re-infection (Balthesen *et al.* 1993). Some 92% of young children with pneumonia in Papua New Guinea had CMV antibodies, although only 1% had a 4-fold rise in antibody levels (Shann *et al.* 1986). Indeed, the range of lung infections (and possible misdiagnoses) increased after the 2002 and 2007 outbreaks in England, including upper and lower respiratory tract infections, unspecified pneumonia, presumed influenza, unspecified bronchitis, bronchiectasis, unspecified COPD, and other interstitial pulmonary diseases and respiratory disorders (Jones 2010k-m). In both adults and children viral infection is one of the most common reasons for re-admission to hospital for asthma (Kuo *et al.* 2001) and, given the increased susceptibility to infection surrounding each outbreak, the possibility of CMV active infection as an underlying risk factor should be investigated.

Neuropathogenesis resulting from CMV infection of the developing fetus is well recognized (Cheeran *et al.* 2009). However, a range of neuro-inflammatory symptoms have also been observed to increase in emergency hospital admission for adults following the 2002 and 2007 outbreaks in England, including migraine and headache syndromes, post-procedural nervous system disorders, disorders of the optic and facial nerve, unspecified convulsions, abnormal involuntary movements, CNS degenerative and movement disorders. The study of neuro-inflammation is a developing area (Majde 2010). Immune function in the CNS is largely regulated by the microglia, which are responsible for phagocytosis, non-specific inflammation and adaptive immune responses, and dis-regulation of microglia is presumed to lead to the neurological disorders (Aloisi 2001). CMV is known to enter microglia, but does not progress to a productive infection (Cheeran *et al.* 2009). The gene expression implied by the multiple and adaptive roles of the microglia could render these cells open to DNA microcompetition, leading to defective gene expression (Polanski 2004). Disorders arising from direct infection of astrocytes, in which CMV establishes a productive infection, are also possible (van der Pol *et al.* 1999; Cheeran *et al.* 2009). All other CNS cells exhibit a similar range from the potential for DNA-based microcompetition through to active infection. Another route to neuroinflammation comes from the observation that neural precursor cells are produced in the hippocampus even in adults. In adult mice the induction of an adaptive immune response with T-cell activation leads to a transient increase in the proliferation and neogenesis of these neural precursor cells (Wolf *et al.* 2009). Human CMV is known to inhibit differentiation of neural precursor cells into astrocytes and to induce their apoptosis (Odeberg *et al.* 2006; Odeberg *et al.* 2007).

While it has been observed that pediatric (children up to the age of 16) admissions do not generally follow the step-changes observed in adults (Jones 2009i), the CMV hypothesis should not preclude an increase in admissions associated with the primary or secondary effects of CMV infection in very young patients. Evidence that this may be occurring is

presented in Figure 4.4, where a time trend from Northern Ireland for infants under the age of one year shows a large spike in admissions for any diagnosis associated with an infection, such as tonsillitis, respiratory tract infections, and viral infections, in the year immediately following the mid-2002/03 and mid-2007/08 outbreaks seen in Northern Ireland (Jones 2010m). This observation is consistent with the observation that CMV infection in the very young remains active for around 8 to 29 months post infection, and that this is due to a selective deficiency in the $CD4^+$ T-cell response to CMV in children (Tu *et al.* 2004). It would appear that further study is warranted to determine whether these admissions are for neonates conceived during the outbreak, or are secondary infections in infants arising from primary CMV infection during the outbreak. In Northern Ireland, the outbreak was noted to occur in October of 2002 and 2007 (Jones 2010m) and hence, conceptions around that point would appear in the 2003/04 and 2008/09 financial year data.

Does the Incidence of CMV Fluctuate over Time?

If the CMV hypothesis is correct, it should be possible to detect fluctuations in the proportion of CMV seropositive individuals. Given the generally observed 10% increase in medical admissions associated with each outbreak, it is possible to estimate the degree of change in CMV-infected individuals. In England, there are around 4.2 million emergency medical admissions per annum, so a 10% step-change would involve some 420,000 extra admissions (persons). The adult population of England is in excess of 42 million so we have an implied 1% (minimum initial) increment in the level of infected adults. If the outbreak is due to the emergence of a new strain, the level of CMV seropositive individuals may not necessarily increase by 1% since infection with multiple strains is possible and the common tests for CMV seropositivity are not strain specific. A 1% seroconversion rate is at the lower end of most published studies (Hyde *et al.* 2010), although one study over an 11-year period in Germany covering healthy blood donors had an average rate of 0.46% with maximum of 1.33% in the 30-35 age group (Hecker *et al.* 2004). The proposed 1% rate is therefore feasible for the emergence of a new strain, as the known seroconversion rate is sufficient to spread a new strain to the required numbers of individuals, especially as children are known carriers of viral and other infections to their elderly relatives (Braunstein and Mandal 2008).

The first piece of evidence comes from a study conducted in Spain, which occurred around the time of the 1993 outbreak. Samples were collected between October 1993 and February 1994, immediately after the March 1993 outbreak observed in the UK, and again six years later between September 1999 and May 2000. CMV seroprevalence was lower in all age groups in 1999/00 compared to 1993/94, especially in the 6-10 and 31-40 age groups, and least in the 2-5 year age group (de Ory *et al.* 2004). This appears consistent with the hypothesis of a CMV outbreak in early 1993 and not immediately prior to or during September 1999 to May 2000. Unfortunately, we have no retrospective hospital admission data against which to test the effect on medical admissions.

Another study conducted in England concluded that, in the interval 1991 to 2002, CMV seropositivity was highest in children born between 1985 and 1989 (Vyse *et al.* 2009). This appears to link back to a suspected outbreak around 1986, observed in Scotland as a step change in the emergency admissions (Kendrick and Conway 2003a-c), in accident and

emergency attendances in early 1987 in England (Jones 2010h), and in total health care costs around 1986 in the USA (Jones 2010f). The somewhat wide time bands employed in this study prevent more detailed conclusions, but expectant mothers are a known high risk group for either primary CMV infection or secondary infection with a new strain (Schoenfisch *et al.* 2011).

A further study in the USA using broad seven-year time intervals of 1988-1994 and 1999-2004 showed generally higher seroprevalence in 1988-1994 for 15 out of 25 demographic types, with age 40-49 being the only group to reach statistical significance (Bate *et al.* 2010). Since both time intervals overlap periods where a number of unexpected step-like shifts in the cost of health care occurred in the USA (Jones 2010f), it is not possible to reach any concrete conclusion; this publicly available dataset should be subject to re-analysis using single-year increments as part of the process of validating this hypothesis.

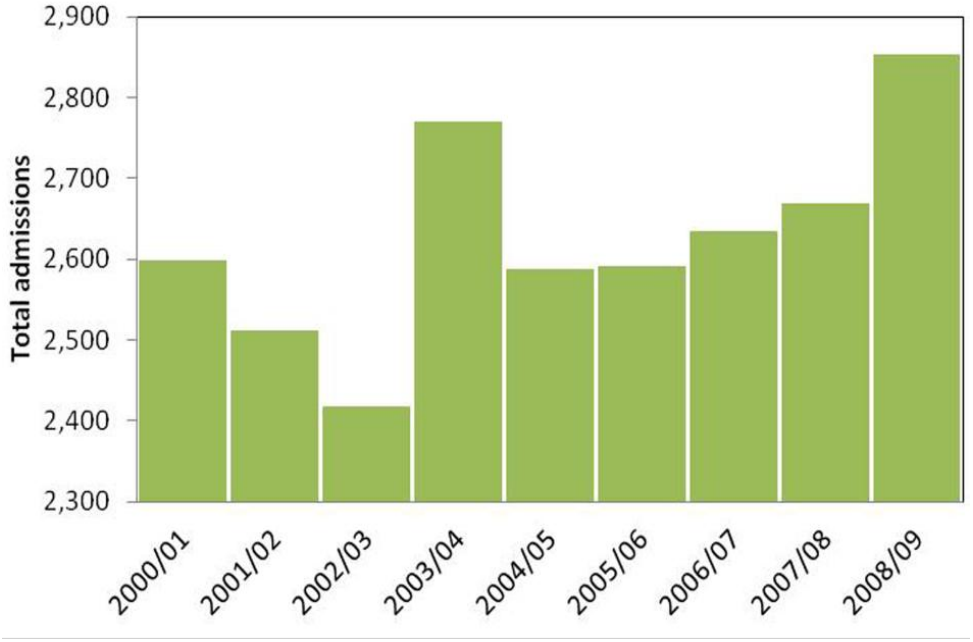

Figure 4.4. Admissions for young children aged less than 1 in Northern Ireland. Data for Northern Ireland were kindly provided by the Information and Analysis Directorate of the Department of Health, Social Services and Public Safety (DHSSPS). Admissions are for any diagnosis in which infection is implicated. Based on Poisson statistics, the 2003/04 spike represents a 5.2 standard deviation difference over the average of the previous three years, and 2008/09 represents a 4.5 standard deviation difference over the average of the previous four years. In both instances the spike represents an approximate 10% increase.

Lastly, a comprehensive review of seroconversion rates among similar risk groups by Hyde *et al.* (2010) shows sufficient variation in conversion rates, owing to the studies being conducted throughout a 40-year time period with a variety of shorter and longer sample periods, to suggest that time-based variation is a real possibility. Populations starting at a similar proportion of seropositivity showed at least a 7% range in conversion rates, which is well above the level of a 1% change needed to initiate the required increase in hospital admissions.

Establishing the validity of the hypothesis will therefore require the collection of statistically significant numbers of samples across multiple age groups at intervals of around one year, particularly in the older age groups (age > 60 years) where the bulk of the increase in emergency admissions occurs. Sampling from those with or without emergency hospital admission will also be required, and levels of CMV antibodies and/or other quantitative measures for active or low level multiplication would be useful additional information.

Synergistic Infections

While the bulk of our understanding of the immunological effects of CMV have come from *in vitro* studies (Boeckh and Geballe 2011), it is important to realize that infection with multiple persistent viruses (CMV, EBV, HSV, etc), bacteria and fungi is common among the population, where multiple and additive immune impairments from the persistent flora interact with the existing immune impairments in the host. In addition to this are the immunological challenges posed by common recurrent infections (influenza, rhinovirus, RSV, etc) and subsequent opportunistic bacterial infections (Baranek and Dalod 2008). For these reasons, it has been an enduring challenge to separate out the role of CMV as the direct agent, risk factor or opportunist. However, it is hoped that, by viewing the totality of immune impairments, the role of CMV can be seen in the wider context as a direct agent of disease (under a wider variety of circumstances than has been formerly appreciated), and as a general immune eroding force with effects that are cumulative with age.

Re-evaluation of Published Time Series

The re-evaluation of published time series for specific diseases may give further confirmation, especially where immune function is implicated in the ultimate expression of the disease. For example, admission for anaphylactic shock in England showed a distinct step change in 1993/94 (at the point surrounding the March 1993 outbreak) compared to the 1992/93 financial year (Sheikh and Alves 2000). A study on the use of ambulance services from 1988 to 1996 showed evidence for a step change around 1993, which appeared to be specific to medical conditions (Wrigley *et al.* 2002). A distinct cyclic pattern can also be observed in the trends for asthma (Anderson *et al.* 2007). Such re-evaluation is required simply because researchers were not aware of the possibility of step changes in the time series and tended to employ linear trends in the analysis of ‘growth’. Indeed, ignoring this very possibility led Blunt *et al.* (2010) to reach the incorrect conclusion that the increase in emergency admissions in England between 2004/05 and 2009/10 was simply due to acute hospitals reducing their threshold to admission – which fails to explain the trends in occupied bed days shown in Table 1 and the wider international synchrony between outbreaks.

Conclusion

Advances in medicine are via observation and the formulation of a plausible clinical hypothesis. The hypothesis presented here requires further research to establish the exact role(s) for CMV, and to consider appropriate public health measures as the solution to the real root cause. This will require longitudinal studies of the levels of inflammatory cytokines in the hospitalized and non-hospitalized cohorts, and corresponding levels of CMV-specific antibodies, with a particular focus on elderly age groups and possibly different racial groups and/or groups with specific gene mutations. Measurement of antibody levels should also be associated with other tests capable of detecting low grade virus replication in different sites (quantitative detection of viral DNA in urine, saliva and other body fluids and/or quantitative detection of viral antigens/DNA/RNA in tissues when biopsies are available). The curious dichotomous immune response to CMV in the presence of particular immune impairments (MS and the APOE epsilon-4 genotype) needs to be more widely recognized as a potential confounding factor.

While many of the studies on the rise in emergency admissions have sought to implicate social trends such as the breakdown of the family unit and the elderly living alone as the primary cause, it is perhaps better to suggest that they are contributory rather than causative factors, and might have only acted to amplify the effect on the medical emergency admissions. This amplification, along with the low levels of influenza over the nine years from 2000 onward, has probably helped to bring the basic root cause to light.

The possibility that age at previous exposure(s) may be important implies that the traditional use of age standardization (usually with five-year age bands) may be acting to obscure what are effectively cohorts of patients moving forward in time, and researchers need to be alert to this possibility.

The possibility of new strains emerging is very real. For example, the emergence of a new strain of the West Nile Virus (WNV) in the USA in 1992 has been implicated in the rapid spread of WNV throughout the North American continent subsequent to that date (Lindsey *et al.* 2010: McMullen *et al.* 2011). If at all possible, the proposed emergence of a significant new strain of CMV in the early 1960s needs to be confirmed (Jones 2010f).

Whatever the cause, the agent is ‘highly infectious’ in the sense that the local medical admission rate moves rapidly from a lower to a permanently higher rate in a matter of weeks, and has enormous implications on the financial pressures faced by health services around the world. If the above association with CMV is correct, then the search for an effective vaccine against CMV needs to be accelerated, as this virus may be responsible for billions of dollars of international healthcare expenditure. The trends in healthcare costs, bed demand and admissions are certainly not acting in the way they are ‘supposed’ to behave and, at the present, the CMV hypothesis is the best starting point for further investigation. In order to have the necessary research programmes in place to track the outbreak and its causes, all concerned need to be alert to the fact that the next outbreak is likely to occur in the interval 2012 to 2016.

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