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INTERNATIONAL OUTBREAKS OF A NOVEL TYPE OF INFECTIOUS IMMUNE IMPAIRMENT: A CALL TO ACTION

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Introduction

In 1993 the National Health Service (NHS) in the UK experienced a large and unexplained increase in medical emergency admissions. This was repeated in 1996 and 1999. Everyone concerned were mystified, numerous letters to the editor of the British Medical Journal were published as doctors sought to understand possible reasons, and academics leapt to analyse possible causes. Unfortunately, no one thought to look for evidence of spatial spread and in the absence of this critical piece of evidence the conclusion was reached, largely without evidence, that the increases were due to the failures of health and social care to contain rising demand [1].

However, people do not generally present to hospital as an emergency admission without real cause, and the mystery surges have continued to occur on a reasonably regular basis. Another such surge occurred in 2016 leaving both the NHS and social care overwhelmed. Demand has been so high that patients have been accommodated, some dying, in hospital corridors, and numerous articles have appeared in the national newspapers seeking to understand possible causes. Everyone has seemingly forgotten the events in the 1990's [1; 12].

For the past eight years' this author has been investigating these curious events to seek fundamental answers as to why human health seems to so rapidly deteriorate during these events. A concise overview of the research conducted to date will be given, followed by more detail surrounding issues of special interest.

Overview of Research

A concise summary of the research to date will now be presented [See 1–30]:

— Deaths (all-cause mortality), medical admissions, NHS staff sickness absence, an increase in the gender ratio at birth, an increase in stillbirths, and an increase in occupied bed days for certain conditions in pregnancy, in neonates, and for certain congenital malformations all rise over a short space of time.

— The increase in the gender ratio and associated pregnancy/stillbirths/congenital malformations appear to initiate first (allowing for the lag due to gestation), next medical admissions rise and finally deaths.

— Research by others regarding spontaneous loss of the female foetus indicates that the effect on the gender ratio must occur between weeks two and fifteen after conception, since higher male spontaneous loss occurs at all other times.

— Only certain conditions are effected, however, the list of conditions affected is surprisingly long. See Table 1 and [2]. The only common link appears to be general increased unwellness; leading to increased clumsiness (falls, fractures, injuries), increased infections, and increased inflammation resulting in condition exacerbation.

— However, while there are large national events [1; 4; 28–30], small area analysis shows mini-outbreaks of a seeming infectious agent which occur in around 1% of small areas at any point in time. There is an approximate two-year interval between outbreaks in any location. Males and females behave as separate compartments.

— The levels of increase in deaths and medical admissions in small areas are alarmingly high.

— Larger national events seem to occur at three to six year intervals with females especially prone to higher death and medical admission. See Fig. 1. However, in 2012, 2014, 2016 large events have occurred with unusually high synchrony between locations.

— The highly unique feature is that the effects against human health endure for approximately one year, hence, running (rolling or moving) 12-month totals/averages act as a specific frequency fil-

Table 1

Increase in Occupied Beds for High Volume Primary Diagnoses Seen During National Outbreaks of the Presumed Infectious Agent

ICD-10	Description	Average bed days	Ratio1, %	Ratio2, %	99% CI
R69	Unknown and unspecified causes of morbidity	2,245,399	17	14	0.2
J18	Pneumonia organism unspecified	2,204,895	11	16	0.2
N39	Other disorders of urinary system	1,494,871	17	2	0.2
P07	Disorders relating to short gestation and low birth weight	573,077	8	6	0.4
A41	Other septicaemia	473,588	18	36	0.4
N17	Acute renal failure	440,274	17	11	0.5
L03	Cellulitis	432,191	17	8	0.5
K80	Cholelithiasis	359,146	7	2	0.5
F60	Specific personality disorders	340,196	7	8	0.5
J69	Pneumonitis due to solids and liquids	327,613	27	21	0.5
S06	Intracranial injury	296,766	15	16	0.6
S32	Fracture of lumbar spine and pelvis	273,530	11	4	0.6
K56	Paralytic ileus and intestinal obstruction without hernia	271,712	8	6	0.6
I61	Intracerebral haemorrhage	254,930	16	4	0.6
K85	Acute pancreatitis	201,074	9	3	0.7
K92	Other diseases of digestive system	191,132	5	1	0.7
K70	Alcoholic liver disease	181,427	17	4	0.7
E87	Other disorders of fluidelectrolyte and acid-base balance	169,651	23	15	0.7
C78	Secondary malignant neoplasm of respiratory and digestive organs	159,174	4	1	0.8
E11	Non-insulin-dependent diabetes mellitus	157,782	17	5	0.8
J45	Asthma	147,005	5	5	0.8
N18	Chronic renal failure	141,487	7	39	0.8
C92	Myeloid leukaemia	133,127	1	5	0.8
I95	Hypotension	129,587	18	2	0.8
F50	Eating disorders	125,246	9	5	0.8
I35	Nonrheumatic aortic valve disorders	122,205	14	3	0.9
A04	Other bacterial intestinal infections	121,681	25	1	0.9
86	Osteomyelitis	121,307	7	23	0.9
N13	Obstructive and reflux uropathy	119,826	5	13	0.9
K83	Other diseases of biliary tract	119,730	7	16	0.9
I60	Subarachnoid haemorrhage	116,173	9	6	0.9
I70	Atherosclerosis	113,181	7	21	0.9
S22	Fracture of rib(s), sternum and thoracic spine	96,279	8	16	1.0
M51	Other intervertebral disc disorders	94,884	1	2	1.0
K50	Crohn's disease [regional enteritis]	93,422	6	2	1.0
C25	Malignant neoplasm of pancreas	90,982	8	3	1.0
K91	Postprocedural disorders of digestive system	89,485	4	3	1.0

End of table 1

ICD-10	Description	Average bed days	Ratio1, %	Ratio2, %	99% CI
G93	Other disorders of brain	89,357	11	14	1.0
C90	Multiple myeloma and malignant plasma cell neoplasms	89,278	5	2	1.0
J47	Bronchiectasis	85,202	12	6	1.0
L02	Cutaneous abscess, furuncle and carbuncle	83,722	17	5	1.0
J15	Bacterial pneumonia not elsewhere classified	79,671	12	1	1.1
T85	Complications of internal prosthetic devices implants & grafts	77,763	6	3	1.1
K81	Cholecystitis	77,571	1	8	1.1
M48	Other spondylopathies	77,171	22	2	1.1
K43	Ventral hernia	72,709	13	2	1.1
I44	Atrioventricular and left bundle-branch block	71,962	17	1	1.1
D50	Iron deficiency anaemia	71,941	10	4	1.1
I33	Acute and subacute endocarditis	71,635	5	23	1.1
O42	Premature rupture of membranes	69,582	14	1	1.1
K55	Vascular disorders of intestine	68,038	6	10	1.2
S12	Fracture of neck	67,898	17	18	1.2
E16	Other disorders of pancreatic internal secretion	67,668	26	2	1.2
N12	Tubulo-interstitial nephritis not spec as acute or chronic	66,840	4	14	1.2
M00	Pyogenic arthritis	64,437	12	15	1.2
T39	Poison by nonopioid analgesic antipyretic and antirheumatics	63,041	5	6	1.2
S00	Superficial injury of head	62,477	13	4	1.2
C22	Malignant neoplasm of liver and intrahepatic bile ducts	60,228	12	4	1.2
I08	Multiple valve diseases	59,210	7	15	1.2
J84	Other interstitial pulmonary diseases	57,767	14	1	1.2
K65	Peritonitis	56,096	7	7	1.3
M46	Other inflammatory spondylopathies	54,259	15	8	1.3

Footnote. Data is for occupied bed days by primary diagnosis from Hospital Episode Statistics (HES) downloaded from the NHS Digital website. The version of ICD-10 was changed in 2012/13. Ratio 1 therefore applies to the former version of ICD-10 used between 1998/99 and 2011/12 and applies to two large national outbreaks centred around 2003/04 and 2009/10. Ratio 2 applies to the version of ICD-10 used from 2012/13 onward to an outbreak centred around 2014/15. See [29; 30]. The 99% CI has been calculated using Poisson statistics based on the average number of occupied bed days per annum [26].

ter to detect start and end of the events.

— While this is generally true additional disease time cascades appear to arise out of each event.

— Persons with existing neurological conditions such as Alzheimer's and dementia show the greatest increase in death during the events.

— The incidence of certain cancers appears to increase, and hospital admission for aggressive forms of tuberculosis appear to rise after a two to three-year lag.

— Doctors surgeries may act as loci for spread.

— NHS staff sickness absence increases to a greater degree than other government workers suggesting occupational exposure (unpublished).

— Interactions with influenza appear to occur on occasions leading to worse outcomes [27].

A Possible Agent

Based on the range of conditions affected it has been proposed that the immune modifying herpes virus

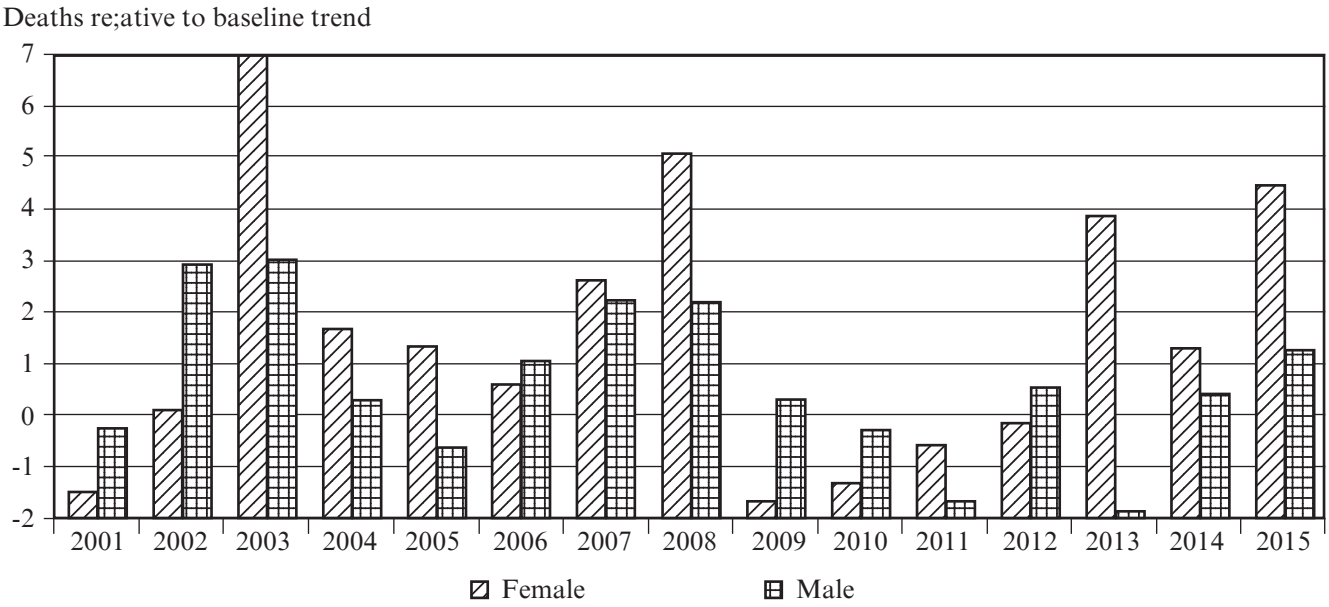

Fig. 1. Trend in deaths in social group 8d2 (Hard pressed ethnic mix) relative to the baseline
Footnote. Data obtained from the Office for National Statistics. Social group 8d2 is especially high in persons of mixed and black ethnicity. Over the period there were an average of 5,900 male deaths and 5,800 female deaths. See ONS [31] for a description of social groups. The baseline trend was approximated by a second order polynomial after removing high years. National level outbreaks in rapid succession in 2012, 2014 and 2016 have led to an estimated 130,000 additional deaths [30]. Full description of methods [26; 27].

cytomegalovirus (CMV) is somehow involved. The reasons for this are as follows [4; 6; 10; 20; 21; 28]:

— CMV is associated with large increases in mortality in populations studies

— Persons with high IgG to CMV show higher rates of decease and disposition to particular diseases

— CMV is now recognised as being both oncomodulatory and oncogenic

— CMV is a common pathogen of the foetus leading to stillbirth and congenital malformations

— CMV can infect a wide variety of tissues, but especially endothelial

— Increases in respiratory disease during the outbreaks is in line with the lung being a major reservoir of CMV

— CMV is now known to exert immune modifying effects even during latency

— CMV appears to potentiate the effect of other pathogens and is seemingly acting as a master controller of the pathogen burden

— CMV is known to interfere with the efficacy of influenza vaccination — especially in the elderly

Immune Competent?

In medical textbooks CMV is widely stated to be only a problem to immunosuppressed individuals [4]. The number of case studies involving severe CMV disease in the supposedly immunocompetent is rapidly expanding. The current definition of immunocompetent may be hindering our appreciation of the wider effects of CMV. For example, individuals who have just undergone intense exercise, sleep deprivation, depressed, obese, pregnant or with diabetes all experience particular types of immune impairment(s) [4]. Indeed, frailty is a commonly overlooked form of immune impairment which influences clinical outcomes [32]. It has been estimated that around 20% of the population are overly sensitive to the outbreaks of the proposed pathogen (CMV??), possibly due to genetic factors or failing immune function toward the end of life [10].

Pathogen Burden

No pathogen acts in sublime isolation. With over 2,200 known human pathogens [33] multiple infection is common. Exposure to 8 of 13 common pathogens is the most common in Mexican Americans [34], and an average exposure to 10 (out of 206 species) viruses, with exposure to 84 species in 0.4% of individuals [35]. The pathogen burden has been associated with increased symptom severity and disease progression in multiple diseases [see reviews 6; 20; 28]. CMV is nearly always identified as a common agent of interest [6; 20; 28], which accords with its ability to modify so many aspects of human immune function [4; 6; 20; 28].

Patients with mixed bacterial and viral (especially CMV) infections experience worse outcome in critical care, presumably the mixed infection leading to the need for admission to the CCU [36]. A CMV/bacterial infection had a 4-times risk of respiratory failure, 6.7-times risk of death, 9.8-times risk of diarrhoea, 10.1-times risk of multisystem organ failure, 67.5-times risk of sepsis and a 218.7-times risk of septic shock [36].

For Clinicians

While CMV exerts its effects in a variety of tissues, overt CMV

Table 2

Common Symptoms of a CMV Infection

Symptom	Comments
Rise in temperature to as high as 41 °C, febrile episodes recur daily, nasopharyngeal and conjunctival irritation, non-productive cough	Common early symptoms
Generalized breathlessness and elevated respiratory rate, pulmonary infiltrates in conjunction with renal and hepatic dysfunction (often in the absence of jaundice or hepatic pain or tenderness). Secondary bacterial infection common.	Common later symptoms
Common symptoms encountered in primary care	Malaise (67%), fever (46%), sweats (46%), aching muscles (36%), respiratory symptoms (28%), arthralgia (17%), headache (14%), Diarrhea (5%). Diarrhea is more common for infections in the gastrointestinal tract. Involvement in appendicitis may be common.
Most common findings	Abnormal liver function tests. 78% of inpatients, 69% in primary care
Age profile	Most frequent age 30–39 in primary care, 20–39 in inpatients. A secondary maximum appears to occur at age 50–59.
Symptom duration	Eight weeks on average but up to 32 weeks
CMV detection	Throat and urine appear generally more successful than blood. Broncholaveolar lavage is possibly the most preferred method. Direct sample from gastrointestinal tract.
Risk factors	Adults and children with neurologic conditions are at higher risk of death and respiratory infection. Crohn's disease and other autoimmune conditions. Elevated Immune Risk Profile (IRP). Asthma, diabetes, emotional/physical trauma, recent surgery, pregnancy, anti-inflammatory drugs, immunodeficiency disorders, cancer and cancer therapy, frailty.
Wider involvement in exacerbation of existing conditions	See Table 1
Potential benefit	Usual anti-virals, CMV-specific CD8+ T lymphocytes, etc. See [39]. High doses of Vitamin D, check blood for any other vitamin/mineral deficiencies

disease of both sub-clinical and clinical nature is widely under-diagnosed. See review [28].

An English study of CMV antibodies in blood samples sent to pathology identified that GPs had 0% success in identifying CMV as the cause of patients presenting for vague or syndromic 'unwellness' [37]. CMV was causative in 2% of random serum samples [36]. Another study identified CMV as the cause of the 'feverish granny syndrome' following a visit from their family [38]. I recently met a previously middle-aged healthy woman who had experienced multiple life threatening hospital admissions, apparently initiated by a sinus infection. CMV was not diagnosed by the hospital doctors but was later confirmed by the requesting the GP to submit blood for CMV serology. See [39] for recommendations for CMV diagnosis and treatment. Table 2 lists common features of CMV disease.

Future Research

The key piece of knowledge required by researchers is that the effect against human health endures for around 12-months. Hence to search for patterns of on/off or high/low switching in any data series. It is preferable to do this separately for males and females as initiation in each can lag randomly behind the other. Any data source can be analysed to detect the presence of these hidden patterns. Research in the UK has seemingly been stifled by a heavy emphasis on policy-based evidence in the NHS [40].

CMV remains a pathogen of considerable interest but this remains to be clinically confirmed. In this respect, assay of blood can be an unreliable indicator of CMV causation and the tissue/organ should be the primary site for CMV immunochemistry. My own preliminary conclusion from the literature is that the relative IgG/IgM response to CMV may differ between males and females.

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Родні П. Джоунс

МІЖНАРОДНІ СПАЛАХИ НОВОГО ВИДУ ІНФЕКЦІЙНОГО ІМУННОГО УШКОДЖЕННЯ: ЗАКЛИК ДО ДІЇ

За останні вісім років зареєстровано спалахи нового виду імунного ушкодження, яке впливає на людське здоров'я в наступні 12 міс. Смертність, частота звернень по лікарняну допомогу, перебування на лікарняному працівників Національної Служби Здоров'я (Великобританія), гендерні показники при народженні, а також показники мертвонародженості та вроджених вад розвитку є чутливими до впливу зазначеного фактора. Хворі на хворобу Альцгеймера та слабоумство мають найвищі показники смертності за подібних умов. У розвитку інфекційного імунного ушкодження встановлена певна роль вірусу герпесу та цитомегаловірусу.

Ключові слова: інфекційні хвороби, цитомегаловірус, імунне ушкодження, смертність, частота звертання до лікаря, мертвонародження.

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Rodney P. Jones

INTERNATIONAL OUTBREAKS OF A NOVEL TYPE OF INFECTIOUS IMMUNE IMPAIRMENT: A CALL TO ACTION

Over the past eight years' evidence has been accumulating for outbreaks of a novel type of immune impairment which appears to affect human health for a period of 12 months before abating. Deaths, medical admissions, NHS staff sickness absence, the gender ratio at birth, rate of stillbirths and congenital conditions are all affected. Persons suffering from Alzheimer's and dementia show the highest deaths during the outbreaks. The common herpesvirus cytomegalovirus (CMV) may be involved.

Key words: emerging infectious diseases, cytomegalovirus, immune impairment, death, medical admission, stillbirth.

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