An edited version has been published as: Jones R (2012) Diagnoses, deaths and infectious outbreaks. ***British Journal of Healthcare Management*** 18(10): 539-548. Please use this to cite.

Diagnoses and deaths associated with a new type of infectious outbreak

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Abstract

Over the years 2002 to 2003 and again in 2007 to 2008 there were up to 31,100 and 23,100 excess deaths respectively across the entire UK. These excess deaths have been linked to the spread of a presumed infectious agent. Analysis of death within 90 days of admission to hospital during 2008/09 reveals that the majority of the excess deaths were associated with just 460 diagnoses (out of 1,380 potential diagnoses associated with deaths within 90 days of admission). Of these 460 diagnoses the main causes for excess deaths (number of excess deaths in brackets) were lower respiratory tract diseases and infections (3,020), symptoms and unknown causes of morbidity (2,940), cancers (750), injury and poisoning (340), diabetes (290), perinatal and congenital conditions (200), mental health & behavioural conditions (170), other infectious diseases (140). Approximately 70% of patients died in hospital. This pattern of diagnoses is consistent with increased hospital admission following recurring events which appear to be outbreaks of a previously uncharacterised infectious immune impairment, hence, an increase in diagnoses related to inflammation or infection including poor outcomes after trauma or anaesthesia.

Key Points

- A spatio-temporal spread of excess deaths within the UK can be demonstrated associated with outbreaks of a presumed infectious agent which commenced in 2002 and 2007.
- Across the four countries of the UK the 2002 and 2007 outbreaks resulted in up to 31,100 and 23,100 excess deaths respectively.
- In England, death within 90 days of admission was associated with around 8,000 to 9,000 excess deaths in 2008.
- Excess deaths were associated with a limited range of diagnoses which are loosely associated with immune function impairment or dysfunction and its consequences.
- Many of these excess deaths could potentially be explained by undiagnosed active infection with the persistent herpes virus, cytomegalovirus (CMV).
- This virus both causes specific immune impairments and re-activates after other immune shocks such as trauma, anaesthesia, cancer treatment or infection leading to death via CMV viremia (unhindered viral replication).
- Further research is urgently required, however, in its own right CMV is probably seriously under-diagnosed in acutely ill patients who are then exposed to increased risk of death.

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Introduction

It has been recently reported that in England around 8,000 excess deaths occurred in 2003 and 2008 and that this appears to be linked to an event which may be a previously unidentified infectious outbreak (Jones 2012b-e). The increase in deaths appears to be associated with a permanent 10% to 15% increase in medical admissions (with an associated cluster of diagnoses), a 10% to 25% increase in GP referrals (depending on location) to a range of specialties along with increases in A&E attendance, ambulance journeys and wider healthcare costs (Jones2012b-e). Based on the cluster of diagnoses associated with increased hospital admission the causative agent has been tentatively proposed to be the ubiquitous herpes virus, cytomegalovirus (CMV) which exerts powerful immune modulating effects and becomes a powerful pathogen when presented with a range of immune impairments and immune deficiencies (Jones 2012e). If the excess of deaths are indeed of an infectious origin then it would be expected that the majority of the excess deaths should be associated with a prior hospital admission. This paper examines the evidence for spatio-temporal spread of excess deaths arising from the 2002 and 2007 outbreaks and investigates a cluster of diagnoses associated with excess deaths in 2008/09, which occurred within 90 days of an admission to an English hospital. The analysis aims to see if there is consistency with the findings referred to above and to explore if the proposed association with CMV is feasible.

Methods

Deaths (all cause mortality) per calendar year in the interval 2000 to 2009 for a variety of regions across the UK were obtained from the Office for National Statistics (England & Wales), National Records of Scotland and the Northern Ireland Statistics and Research Agency. The trend in death for each location was plotted and the years with higher deaths were visually identified (usually 2002, 2003, 2007, 2008) and then removed from a polynomial regression (Microsoft Excel) to determine the background trend in the absence of the two infectious outbreaks which initiated in 2002 and 2007. The trend for deaths in Northern Ireland required splitting the data into two parts; first part used deaths between 1997 and 2003 while the second used deaths between 2004 and 2009. A polynomial has been used since deaths were due to level off around 2009 (earlier in Northern Ireland) the net result is a non-linear trend. Actual deaths were then compared to the 'expected' deaths

calculated from this regression. This method is designed to estimate the upper limit for excess deaths which are presented as a percentage higher than expected.

Death in the financial year following an admission to hospital in England was derived from the Hospital Episode Statistics (HES) website from the 'Summary of deaths following admission or primary procedure' table (http://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=1299). This table contains details of deaths within 30, 60 and 90 days of admission and gives the primary diagnosis for the admission. The 90 day table was used on this occasion to cover the widest possible group of persons in the terminal part of their life. Deaths in 2008/09 and 2009/10 have been adjusted upward by 5% and 9% respectively to account for the underlying trend downward in total deaths for England. This trend was determined using a polynomial curve fit to data between 2000 and 2010 for deaths from all causes in England as per Jones (2012e) and will tend to give a conservative estimate of excess deaths. Analysis was conducted at the level of primary diagnosis and any diagnosis having more than 9% higher deaths in 2008/09 was included in the category of 'excess' deaths. Individual diagnoses were aggregated according to the ICD-10 summary level groupings. This method is designed to give a highly conservative estimate of excess deaths and to avoid false positive identification; hence the groups of diagnoses identified have the highest possible methodological and statistical significance.

Spatio-temporal Spread

As mentioned in an earlier study of the volatility associated with deaths in different locations, it is difficult to conduct statistically significant analysis for regions having less than 10,000 deaths (Jones 2012b). Analysis has therefore been restricted to the 23 largest parts of the UK including the separate countries in the Union and the largest regions and counties. It has also been suggested that each outbreak commences with an initial modest burst of increased deaths for around 6 to 8 weeks followed by somewhere between 9 to 12 months of prolonged higher daily deaths (Jones 2009, 2012b). Hence the net effect on deaths will depend on the timing of introduction and then subsequent spread. Deaths are therefore expected to be higher over one or more years.

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The next issue is assessing the level of 'excess' deaths. While there are alternative measures of excess winter deaths (Jones 2012b), this study has made use of two factors. Firstly, over the period 2000 to late 2009 influenza activity was at a 100 year minimum (Jones 2012b,e). The H1N1 (swine flu) pandemic in late 2009 also had a very modest impact on deaths in the UK. This period therefore gives an unhindered view of any alternate outbreaks. With this in view, a visual inspection of the various regional trends show that apart from the years 2002/2003 and 2007/2008 (and sometimes 2008/2009) the other years tend to fall along a curved line with a downward slope consistent with the on-going reduction in the number of deaths, which has been occurring since around 1999. Hence, as presented in the methods section the 'excess' deaths reported here are relative to this background trend which has been characterised via polynomial regression ($y = a + bx + cx^2$).

Table One: Spatio-temporal pattern of deaths across the UK

Location	Deaths in 2009	Excess Deaths (%)					95% CI	
		2002	2003	2007	2008	2009	2002/03	2007/08
Tyne & Wear	11,067	2.3%	3.1%		5.6%		2.0%	2.0%
Hampshire	11,269	2.9%	4.9%	2.6%	2.7%		2.0%	2.0%
Lancashire	11,886	2.4%	4.4%	1.6%	3.5%		1.9%	2.0%
Essex	12,440	1.2%	1.6%		2.0%		1.9%	1.9%
South Yorkshire	12,672	1.8%	2.6%	2.2%	2.8%	0.5%	1.9%	1.9%
Kent	13,698	1.0%	3.6%	0.3%	0.1%	1.4%	1.8%	1.9%
Merseyside	14,162	1.9%	3.8%	2.7%	3.6%		1.7%	1.8%
Northern Ireland	14,445	0.8%	0.6%	1.6%	3.2%		1.8%	1.8%
West Yorkshire	19,149	3.2%	1.5%	2.4%	4.5%		1.5%	1.5%
West Midlands (County)	23,149	0.5%	4.0%	0.8%	3.1%		1.3%	1.4%
Greater Manchester	24,025	1.6%	3.8%	0.9%	2.6%		1.3%	1.4%
North East	26,011	1.1%	2.9%		3.9%		1.3%	1.3%
Wales	31,006	1.6%	4.1%	2.7%	3.1%		1.2%	1.2%
Outer London	32,712	2.0%	5.6%		1.5%	0.4%	1.1%	1.2%
East Midlands	40,880	1.6%	4.2%		2.7%		1.0%	1.1%
London	48,551	1.6%	4.7%		2.2%		0.92%	0.98%
Yorkshire & Humberside	48,625	2.1%	2.9%	2.2%	3.3%		0.96%	0.98%
West Midlands (Region)	50,094	0.2%	3.5%	0.9%	3.0%		0.93%	0.96%
East of England	51,066	2.0%	2.7%		2.6%		0.95%	0.96%
South West	52,101	2.3%	4.9%	1.2%	2.7%		0.93%	0.95%
Scotland	53,856	2.0%	3.4%	2.2%	2.6%		0.91%	0.93%
North West	67,937	1.8%	3.3%	1.7%	3.1%		0.80%	0.83%
South East	73,976	1.7%	3.2%		1.9%		0.78%	0.80%
England	459,241	1.7%	3.6%	0.7%	2.7%		0.31%	0.32%
United Kingdom	559,649	1.9%	3.8%	1.2%	2.9%		0.28%	0.29%

Footnote: Regions are ranked from least to highest number of deaths in 2009 as per the second column. The 95% confidence interval (95% CI) has been calculated assuming a Poisson distribution. North East, North West, Yorkshire and the Humber, East Midlands, West Midlands, East of England, London, South East and South West are all former Government Office Regions.

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However, these issues aside, Table 1 presents the evidence that the pattern of excess deaths following both the 2002 and 2007 events behaves in a manner consistent with the spatio-temporal spread of an infectious outbreak, albeit of a relatively difficult to transmit agent (Jones 2012b,e). Spread across each region results in a different shaped profile of excess deaths in the first and subsequent years of each outbreak. Cumulative excess deaths across the UK ranges from 5.4% (quartile range 4.6% to 5.8%) after the 2002 outbreak to 3.9% (quartile range 2.7% to 5.4%) following the 2007 outbreak. Each region has a unique profile over time reflecting the speed and extent of infection throughout the composite geographies subsequent to introduction of the agent. In absolute numbers the 2002 and 2007 outbreaks led to a total of 33,300 and 23,100 excess deaths respectively across the entire United Kingdom. The 2002 outbreak appears to have reached full spread within just two calendar years while the 2007 outbreak may have extended into the third calendar year in parts of Kent, South Yorkshire and Outer London. Note the difference in the profiles for the West Midlands region which has roughly twice the number of deaths as the West Midlands county, which was far more effected especially after the 2002 outbreak. The difference may be due to lower overall population density in the region or point(s) of entry.

The results for the 2002 outbreak will be elevated due to 2,140 excess deaths in England and Wales arising from the August 2003 heat wave which was accompanied by high levels of ozone and particulates. Excess deaths were highest in London, the South and Midlands but not in the North and mainly affected the over 75's (Johnson et al 2005). This however, only accounts for less than 8% of the excess deaths arising after the 2002 outbreak and does not therefore detract from the overall conclusions. A further heat wave in July of 2006 did not appear to unduly increase deaths.

Given that deaths are the pinnacle of much wider morbidity and associated costs the highly variable impact across different regions following the 2002 and 2007 outbreaks goes a long way to explaining the vast differences in financial performance between PCTs which were (incorrectly) attributed to failure of management. The very fact that deaths are increased precludes explanations based on thresholds to hospital admission or for GP referral as neither of these leads to death per se.

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Diagnosis Prior to Death

Having established that the time-profile for deaths are consistent with an infectious spread it is appropriate to investigate the diagnoses associated with patients admitted to hospital prior to death. Analysis of diagnosis prior to death is constrained by the available data; however, as Table 1 clearly demonstrates the use of data covering England for the 2008/09 financial year captures the vast bulk of the deaths due to the fact that 22 out of 23 regions have the maximum deaths in 2008. Earlier analysis identified that there were at least 8,000 excess deaths in the 2008 calendar year (Jones 2012b). Diagnoses associated with excess deaths in 2008/09 for admission to hospital prior to a death within 90 days are shown in Table 2. The majority of the excess deaths were associated with just 460 diagnoses (out of 1,380 potential diagnoses associated with a death within 90 days) and in 2008/09 this group accounted for 11.5% of total deaths and 11.7% of deaths in hospital. For this group 71.4% of deaths occurred in hospital compared to 69.9% in the larger group having no excess deaths. Of these 460 diagnoses the main causes for excess deaths (number of excess deaths in brackets) were lower respiratory tract diseases and infections (3,020), symptoms and unknown causes of morbidity (2,940), cancers (750), injury and poisoning (340), diabetes (290), perinatal and congenital conditions (200), mental health & behavioural conditions (170), other infectious diseases (140).

The analysis of death following admission to hospital using the HES data is subject to a source of methodological bias for people having more than one finished consultant episode (FCE) for whom the death will be counted multiple times. In 2007/08, 2008/09 and 2009/10 there were 14%, 14.7% and 15.6% more FCE than admissions respectively. This does not materially affect the analysis of excess deaths presented here but implies that the real number of deaths will be around 15% lower than reported in Table 1. Hence the 8,100 excess deaths examined declines to 7,050 – although a high cut-off of 9% more deaths in 2008/09 has been applied to avoid complicating the analysis with diagnoses of marginal statistical significance. This is still very close to the figure of around 8,000 excess deaths observed in 2008 (Jones 2012b). From this we can infer that the analysis has captured the majority of the significant events and that hospitalisation prior to death was a common occurrence.

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Immune Impairment

Given the proposal that the excess deaths could be due to an outbreak of cytomegalovirus (CMV) and associated immune impairment it may be appropriate to see if this is clinically possible and if it concurs with the diagnoses listed in Table 1. CMV is a relatively common virus and leads to life-long infection with recurring re-activation (as in other herpes viruses). In England & Wales, 15% of children aged 1 to 4 are infected and this increases to 80% for those aged over 65. The incidence of infection in children is higher in particular years (Vyse et al 2009). CMV is unique in that it occurs as multiple strains which are capable of re-infecting an individual multiple times and this has been proposed to account its ability to exploit a wide variety of temporary immune impairments (via injury, cancer, infection, gene mutations, stress, etc) in multiple organs – retina, liver, lung, gastrointestinal tract, vascular system including atherosclerosis, coronary artery disease, endothelialitis, coronary restenosis and inflammatory aortic disease (Presti et al 1998, Jones 2012e). Without listing the references, it should be noted that clinical case reports for CMV infection as the primary cause of both fatal and non-fatal hospital admission are becoming increasingly common as awareness to the subtle and multiple clinical effects (fever, cough, wheezing, nausea, diarrhoea, granulomatous hepatitis, urinary tract infection, impaired hepatic and renal function) of this virus increases. The virus typically re-activates up to six weeks after trauma, other infections, cancer treatment, surgery/anaesthesia, administration of anti-inflammatory drugs, etc (Coulson et al 1974, Heininger et al 2000, Heininger et al 2011). A recent review of cases in which CMV was diagnosed in immunocompetent patients indicates approximately 6% mortality, which increases above the age of 55 (Rafailidis et al 2008). Another study of 209,695 hospitalisations for immunocompetent patients identified a group of viruses associated with poor outcomes (CMV, herpes simplex (HSV), influenza and respiratory syncytial virus) where patients with a bacterial plus viral infection had a 6.6-times higher risk of death, 8.3-times risk of multi-organ failure and 271-times risk of septic shock (Miggins et al 2011). Both highlight the issue of under-diagnosis and lack of awareness to the importance of CMV infection or co-infection, all of which is very well known in the extreme setting of hematopoietic stem cell transplantation.

Factors indicative of a role for CMV in higher than expected mortality consistent with the multiple diagnoses in Table 1 are as follows: CMV seropositivity is associated with all-cause

mortality with a hazard ratio of 1.19 (95% CI: 1.01-1.41) while CMV infected individuals with elevated C-reactive protein (an inflammatory marker) have a 30.1% and 29.5% higher risk for all-cause mortality and cardiovascular disease-related mortality in the 14,000 subject NHANES-III study with 10-year follow-up (Simanek et al 2011); CMV has been detected in 15% of over 20 week stillborn and congenital mortality shows regional differences (Bristow et al 2011, Iwasenko et al 2011); the lung is a frequent site of infection and acute respiratory infections are statistically significantly more frequent in CMV infected children, although death is probably restricted to the elderly rather than children (Chomel et al 2001); CMV colitis should be considered in the elderly with diarrhoea or as primary cause in those with urinary retention (Michaelson et al 1983, Lin et al 2010); in patients suffering from burns CMV reactivation has been reported in 50% of patients and a further 20% suffer a primary infection with the virus (Rennekampff & Hamprecht 2006); CMV is a serious risk factor in those with rheumatic and other autoimmune diseases (Posnett & Yarilin 2005, Einstein & Wolf 2010); for those with cancer CMV pneumonia is associated with a significant number of deaths [per 1000 in brackets]: multiple myeloma [18], brain [10], undifferentiated solid tumours and non-Hodgkins lymphoma [7] (Mera et al 1996) while general mortality in cancer patients with CMV viremia can be as high as 70% (solid tumors) to 32% (haematological), rising to 75% for those needing mechanical ventilation, although 60% survive if CMV is diagnosed and antiviral treatment is initiated (Wang et al 2011); in children undergoing cancer treatment some 35% have an active CMV infection – primary infection in the youngest and re-activation in the older (Michalek and Horvath 2002); for those with severe sepsis and septic shock CMV reactivation (with knock-on HSV reactivation in around 70% of patients) is associated with up to 60% mortality, and around a 20 day increase in length of hospital stay including increased stay on mechanical ventilation (Ho 1998, von Muller et al 2006,Heininger et al 2011); CMV is a source of inflammation in the eye and surrounding tissue (Zoukhri 2006); immune system disorder is associated with both minor and major depression in medically ill older adults (Koenig 1997); for those with HIV/AIDS but not receiving antiretroviral therapy, CMV viremia (>1,000 copies per ml) gives an odds ratio for death 3.4 higher than those without (Fielding et al 2011) and finally fatal mini-epidemics have been reported in transplant units (Coulson et al 1974), geriatric departments (Shats et al 1998) and in neonatal intensive care units (Gurevich & Cunha 1981).

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While this list is not exhaustive it does indicate that it is clinically possible for CMV to lead to excess deaths across the spectrum of diagnoses listed in Table 1. Indeed since 50% of deaths in 2008 in England and Wales occur above age 77 in men and 84 in women the observation that around 40% of the elderly (age 70-92) have signs of *active* CMV infection is highly relevant (Musiani et al 1988). Much of the above has been known for many years, indeed many of the studies date back to the 1980's. However the known potential for cytomegalovirus to cause acute and chronic disease has only recently received the attention it deserves (for reviews see Posnett & Yarilin 2005, Britt 2008, Varani & Landini 2011, Jones 2012d, Pawelec et al 2012) and significant under-diagnosis is highly likely. Other explanations may be possible and need to be investigated. For example, CMV may be re-activated by other infectious agent(s); however, for the moment either primary infection with a new strain of CMV or re-activation in response to other factors appears to be a good candidate to offer some explanation for the excess deaths.

The large number of excess deaths attributable to unknown causes of morbidity and to signs and symptoms arises from two sources. Firstly, case notes for those who die in hospital are usually transferred to the coroner's office and this can lead to a default code. Secondly, given the multiplicity of vague symptoms which can arise from CMV infection a definitive diagnosis is often elusive, even more so in the elderly, especially given the relative low risk usually assigned to this virus (jones 2012e).

The potential for CMV 'outbreaks' is highly feasible since all persistent infections exist in a state of continuous 'outbreak' where the interplay between environment, population immunity and statistical fluctuation in transmission rates create the potential for larger 'outbreaks'. The emergence of new strains only increases this risk. The 10% to15% increase in medical admissions which appears to accompany each outbreak implies that somewhere higher than 1% of the total population has either newly acquired CMV (or the equivalent CMV reactivation). For example, in one study of 24,260 healthy blood donors over 11 years *average* infection with CMV for the first time (seroconversion) was 0.55% per annum (± 0.1% as 95% CI assuming simple Poisson randomness), although this was higher in women and for age 30-35 was 1.33% (Hecker et al 2004). Seroconversion of higher than 1% is also well within the known time-based variation in proportions of population known to be

infected with CMV (Jones 2012e). Even less than these appear to go on to create the 8,000 excess deaths, hence the main impact is upon population morbidity rather than mortality.

Conclusions

The implication of these findings to benchmarking hospital deaths should also be apparent both in terms of the particular years used to prime the models and the points in time at which different hospitals are compared against the model. In this respect, a study which developed a method to predict seven day mortality following emergency medical admission (Goodacre et al 2012) used data to derive the model from three sites in the UK over the period November 2007 to May 2008 and validation from sites in England, Hong Kong and Australia over the period September 2008 to July 2010. Hence both derivation and validation phases overlap the period of the outbreak in the UK and Australia (unpublished). These overlaps may partly explain why hospital specific model coefficients performed better in the validation phase. Given the suggested international nature of these outbreaks it is of interest to note that in the USA death following complications of surgical or medical care also show peaks in 2002 and 2008 (with a shoulder in 2007). The magnitude of these peaks increase with age and are especially prominent for those aged over 75 years (CDC Quick Stats 2012).

Whatever the ultimate cause for the excess deaths it is highly likely that CMV (as a causative or complicating factor) was greatly under-diagnosed and that antiviral therapy would have prevented some of these deaths. The initial findings appear to indicate that it is indeed feasible that CMV (via introduction of a new strain or re-activation of existing infection) may be related to the recurring events, which increase inpatient admission and death.

It is also clear that the regional profile of deaths is sufficiently variable to indicate that the financial pressures arising out of each outbreak will create disproportionate pressures which are not recognised in the current capitation formula or in health service policy. In this respect Surrey is a good example with a 1.9% (0.8% + 1.1%) increase following the 2002 outbreak and 4.5% (2.0% + 2.5%) following the 2007 outbreak. Surrey experienced a late spread with peak deaths in 2009 (analysis not shown) which confirms a late peak in bed occupancy (Jones 2012a). It is highly likely that the efforts of local managers to address these differential pressures may have diverted attention away from longer term and more

beneficial projects. Further research is urgently required in view of the approximate £6 to £7 billion of extra costs, which appear to be associated with each event/outbreak, i.e. it is the associated burden of morbidity that is of even greater concern (Jones 2012d,e). Given that the next outbreak is due in the interval 2012 to 2015 urgent attention to these issues are required in view of the multiple public health, financial and policy implications.

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An edited version has been published as: Jones R (2012) Diagnoses, deaths and infectious outbreaks. ***British Journal of Healthcare Management*** 18(10): 539-548. Please use this to cite.

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Table 1: Excess deaths following admission in 2008/09

ICD-10 Codes and Diagnostic Group	Deaths after admission			Excess Deaths		Significance
	2007/08	2008/09	2009/10	Number	Increase	
R69 Unknown & unspecified causes of morbidity	7,193	8,875	5,337	2,610	42%	>99.99%
J40-J47 Chronic lower respiratory diseases	18,105	19,212	17,022	1,649	9%	>99.99%
J20-J22 Other acute lower respiratory infections	11,437	12,633	11,083	1,373	12%	>99.99%
E10-E14 Diabetes Mellitus	2,150	2,456	2,191	286	13%	>99.99%
T00-T14, T20-T32, S00-S98 Burns, corrosions & injuries	1,088	1,351	1,102	256	23%	>99.99%
Z00-Z13 Examination and investigation	787	917	687	180	24%	>99.99%
C81-C96 Malignant neoplasms of lymphoid, haematopoietic tissue	911	1,028	829	159	18%	>99.99%
C00-C14 Malignant neoplasm of liporal cavity and pharynx	763	936	793	158	20%	>99.99%
C15-C26 Malignant neoplasm of digestive organs	1,156	1,317	1,170	154	13%	>99.99%
R50-R68 General symptoms & signs	631	758	617	134	21%	>99.99%
Z40-Z54 Persons encountering health services for specific care	495	553	352	129	31%	>99.99%
J80-J99 Other diseases of the respiratory system	1,311	1,458	1,355	125	9%	>99.5%
C30-C41, C60-C80 Other neoplasms	639	738	606	115	19%	>99.99%
E15-E90 Endocrine nutritional and metabolic diseases	423	557	469	111	25%	>99.99%
D50-D64 Anaemias	741	983	1,007	109	12%	>99.99%
Q00-Q99 Congenital malformations	164	278	190	101	57%	>99.99%
M30-M36 Systemic connective tissue disorders	258	363	269	100	38%	>99.99%
R70-R94 Abnormal diagnostic findings	742	879	830	93	12%	>99.5%
P00-P96 Other conditions originating in the perinatal period	331	471	436	88	23%	>99.99%
G50-G73, G90-G99 Diseases & disorders of the nervous system	587	634	508	87	16%	>99.99%
C45-C49 Malignant neoplasms of mesothelial and soft tissue	519	663	643	81	14%	>99.5%
D00-D48 In situ & benign neoplasms and others of uncertainty	295	379	308	78	26%	>99.99%
H00-H06, H15-H22, H30-H36, H43-H5 Other disorders of the eye	245	430	473	71	20%	>99.99%
I80-I89 Diseases of veins & lymphatic system	704	809	773	71	10%	>99.5%
Z70-Z76 Persons encountering health services	521	460	264	68	17%	>99.5%
J10-J18 Influenza & pneumonia	493	566	507	66	13%	>99.5%
N20-N23 Urolithiasis	281	323	244	60	23%	>99.99%
K00-K14 Diseases of oral cavity, salivary glands & jaws	213	291	257	55	24%	>99.5%
I10-I15 Hypertensive diseases	279	300	210	55	23%	>99.5%
M80-M94 Osteopathies and chondropathies	90	143	88	54	61%	>99.99%
K40-K46 Hernia	254	324	288	53	20%	>99.5%

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M00-M25 Arthropathies	279	331	283	50	18%	>99.5%
I30-I52 Other forms of heart disease	257	292	231	47	19%	>99.5%
A20-A49 Certain bacterial diseases	352	401	356	47	13%	>99%
R00-R09 Symptoms & signs of circulatory/respiratory system	514	564	523	46	9%	>95%
Z80-Z99 Persons with potential health hazards related to family	25	63	16	43	207%	>99.99%
H60-H95 Diseases of the ear and mastoid process	114	167	135	42	34%	>99.99%
M60-M79 Soft tissue disorders	235	289	258	42	17%	>99.5%
T36-T65 Poisoning	107	150	112	40	37%	>99.99%
H00-H06, H15-H22, H30-H36, H43-H59 Other disorders of the eye etc.	267	285	223	39	16%	>99%
I60-I69 Cerebrovascular diseases	203	211	141	39	23%	>99.5%
T66-T78 Other and unspecified effects of external causes	236	331	352	37	12%	>95%
B15-B19, B25-B34 Other viral diseases	119	158	127	35	28%	>99.5%
L00-L14 L55-L99 Other infections and disorders of the skin	156	206	190	33	19%	>99%
N80-N98 Noninflammatory disorders of female genital tract	171	186	135	33	21%	>99.5%
D65-D89 Diseases of the blood and blood-forming organs	80	111	80	31	38%	>99.5%
N40-N51 Diseases of male genital organs	211	248	228	29	13%	>95%
G40-G47 Epilepsy migraine & other episodic disorders	106	140	116	29	26%	>99.5%
N00-N08, N10-N16 Diseases of the kidney	90	113	87	24	27%	>99.5%
E00-E07 Disorders of thyroid gland	78	100	74	24	31%	>99.5%
K20-K31 Diseases of oesophagus, stomach & duodenum	88	103	71	23	29%	>99.5%
R10-R19 Symptoms & signs of digestive system & abdomen	84	98	69	21	28%	>99%
N25-N29 Other disorders of kidney & ureter	120	143	123	21	17%	>95%
R20-R23 Symptoms & signs inv. the skin & subcutaneous tissue	71	89	73	18	25%	>95%
K35-K38 Diseases of appendix	101	109	82	17	19%	>95%
J00-J06 Acute upper respiratory infections	36	62	54	17	38%	>99%
B00-B09 Viral infections characterized by skin & mucous lesions	68	68	35	17	32%	>99%
F30-F69 Mood, Neurotic, bahavioural & personality disorders	41	54	34	17	44%	>99.5%
I95-I99 Other & unspecified disorders of the circulatory system	188	190	159	16	9%	89%
M40-M54 Dorsopathies	85	96	75	16	20%	>95%
B35-B49 Mycoses	8	22	6	15	215%	>99.99%
N30-N39 Other diseases of the urinary system	54	72	62	15	25%	>95%
O10-O75, O85-O92, O95-O99 Complications of labour and delivery	16	28	13	14	93%	>99.5%
I70-I79 Diseases of arteries, arterioles & capillaries	19	41	36	14	49%	>99.5%
R40-R49 Symptoms of cognition, speech & voice	44	60	49	14	29%	>95%
F20-F29 Schizophrenia, schizotypal and delusional disorders	18	33	22	13	65%	>99.5%

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F04-F09 Other organic including symptomatic mental disorders	59	65	48	12	22%	>95%
N70-N77 Inflammatory diseases of female pelvic organs	39	48	34	12	32%	>95%
L00-L14, L55-L99 Other infections and disorders of the skin	61	71	61	11	17%	92%
T80-T88 Complications of surgical & medical care	53	59	45	10	21%	92%
L40-L45 Papulosquamous disorders (including Psoriasis)	35	53	51	10	23%	93%
F80-F99 Other mental and behavioural disorders	77	80	66	9	13%	86%
J60-J70 Lung diseases due to external agents	4	13	6	8	160%	>99.5%
L50-L54 Urticaria and erythems	29	42	39	8	24%	92%
G00-G13, G30-G32 Other degenerative diseases incl Alzheimer	13	23	17	8	53%	>95%
A65-A79, B85-B99 Other infectious and parasitic diseases	14	19	10	7	58%	>95%
H00-H06, H15-H22, H30-H36, H43-H59 Other disorders of the eye	25	31	24	7	27%	90%
L20-L30 Dermatitis and eczema	1	9	4	7	259%	>99.99%
F70-F79 Mental retardation	14	20	14	6	43%	>95%
A15-A19 Tuberculosis	9	18	16	6	44%	>95%
R20-R29 Symptoms & signs of nervous & musculoskeletal system	32	45	48	5	13%	80%
N60-N64 Disorders of breast	27	32	28	5	16%	82%
A00-A09 Intestinal infectious diseases	3	8	4	5	129%	>99%
H10-H13 Disorders of conjunctiva (including conjunctivitis)	10	13	7	4	52%	94%
F10-F19 Disorders due to psychoactive substances	17	19	13	4	27%	84%
A80-A89 Viral infections of the central nervous system	7	8	2	4	78%	>95%
Z20-Z29 Health hazards related to communicable diseases	5	13	14	4	37%	87%
B50-B83 Protozoal & Helminthial diseases	5	10	8	3	53%	91%
I00-I09 Rheumatic heart disease	17	20	18	3	14%	73%
M95-M99 Other disorders of the musculoskeletal system	4	5	2	2	67%	89%
Total of above	**59,008**	**67,428**	**56,128**	**9,860**	**17%**	**>99.99%**

Footnote: Statistical significance was determined from a Poisson distribution. Excess deaths in 2008/09 are calculated relative to the average number of deaths in 2007/08 and 2009/10. Since Table 1 has identified that there are excess deaths in 2007/08 the 'excess' deaths presented in this table will be an underestimate.