Can time-related patterns in diagnosis for hospital admission help identify common root causes for disease expression?

Rodney P Jones Ph.D.

Healthcare Analysis & Forecasting

Honister Walk, Camberley, Surrey, UK GU15 1RQ

Telephone: +44 (0)1276 21061

Email : hcaf_rod@yahoo.co.uk

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Introduction

Up to the present most healthcare planning has assumed that demography is the primary factor responsible for growth. Rightly or wrongly, large hospitals are built based on this fundamental assumption [1]. The author is not aware of any publication which has actually proved the validity of this approach; however, by default a precedent has been established. It would seem that all concerned have simply assumed that this is the case. It is the author's experience that attempts to suggest to healthcare managers that demography may give unreliable estimates of future demand are met with great scepticism. Such an ideological framework may therefore act to limit the exploration of alternative concepts.

Anyone who has attempted to follow trends in inpatient care over a long time period will be acutely aware that many diagnoses do follow unique trends which are unrelated to any underlying demographic change. These 'unexplained' trends have largely been ignored as data artefacts due to poor coding processes within hospitals or simple random variation. In other words, the expectation of gradual and roughly linear demographic growth leads to the pre-conceived idea of what is considered a 'normal' trend.

Recent research is however beginning to question the validity of this approach. A study in Scotland looking at trends in emergency admission for older people concluded that demographic growth may only explain as little as 10% of the actual long-term increase [2]. Other studies have noted that in some specialties the long-term trends appear to follow cycles while growth in medical admissions appears to involve step-changes [3-7]. Admissions involving 'injury' have been shown to exhibit a unique growth pattern [8].

A recent study comparing trends in emergency admission for a wide range of diagnoses against an assumed linear growth model showed that over 58% of total activity was subject to a high degree of 'special cause' variation and that only 18% could be said to approximate straight line growth in the absence of 'special cause' variation [9]. Special cause variation will include all weather and environmental factors (such as viruses and other infectious agents) influencing the development and expression of poor health and all other sources of non-linear growth [3,10].

The linkage between human health and the environment is widely appreciated. Long term cycles in human longevity, gender ratio at birth and susceptibility to disease have been demonstrated to be linked with the approximate nine year cycle in solar flare intensity [11-16]. Temperature is a fundamental regulator of human health and hence global warming will both increase and decrease the incidence of various diseases and conditions [17]. Global warming itself follows a complex series of short, medium and long term cycles [18] and hence hospital admissions for particular conditions should exhibit the same behaviour. Most infectious diseases show a periodic nature with the time between successive outbreaks being specific to each disease [19-23]. Even common conditions such as appendicitis have shown long term trends which are unrelated to demography and may involve links to factors causing inflammation such as air pollution and viral infection [24-26].

Indeed government policy initiatives can also deliberately or inadvertently lead to trends in admission which are unrelated to demography. The shift in care for a range of mental health conditions from an inpatient to community focussed model is one example of a deliberate change [27-28]. In England, the imposition of targets for an 85% day case rate and a four hour maximum wait for an emergency department visit led to a unique set of inadvertent trends which were more to do with poor adherence to data standards than real growth [29-32]. For both targets the trends uniquely affect 'admissions' where the admission and discharge is on the same day, i.e. zero day stay. Once recognised such factors can be adjusted for in subsequent analysis of trends.

The potential role for viral infection as a basis for both primary and secondary expression of disease is becoming increasingly important. Hence in the case of appendicitis the periodic behaviour over time led to an unsuccessful attempt to correlate with a number of common viral infections [26]. The difficulty lies in knowing where to look among greater than 1,400 possible viral and non-viral candidates [33] and an unknown number of as yet unidentified viral agents [34] all within the context that the potential to cause chronic disease for many viruses still remains largely unstudied [35] or that opportunistic infection can occur subsequent to the initial infection [36].

An alternative approach could be to look for diagnoses showing a similar pattern of admissions over time. These can then be clustered together and common mechanisms explored. In this respect a curious three to six year pattern of step-changes in medical admission has been observed to occur in the UK and possibly elsewhere. The most recent of these step changes occurred around September of 2002 and again in 2007 [3-5]. A previously unrecognised infectious outbreak has been postulated with a mode of action against general immune function [37-38]. A linkage has been suggested with a shift in the Immune Risk Profile (IRP) - poor T cell proliferation and response to mitogens, low numbers of B cells, an inverted CD4:8 ratio caused by the proliferation of CD8 cells and CMV seropositivity - which is involved in the wider decline in health toward the end of life [39-41]. This may have parallels with the higher rate of biological ageing leading to increased susceptibility to infection and inflammation which occurs with AIDS [42].

The aim of this study is to investigate common associations between diseases and conditions which are serious enough to lead to inpatient care. This study presents preliminary evidence for unique time-based changes in diagnosis associated with the step-change in medical admission and demonstrates that the method may have wider application in understanding the potential common linkages behind the unique time trends shown by other diagnoses.

Methodology

Hospital admission data in the UK contains information on the primary diagnosis for each admission which has been coded using the International Classification of Diseases (ICD) 10th revision. Each ICD code commences with a letter denoting a group of conditions or body system followed by three numbers, hence, a full code has four digits. However for the purpose of wider disease classification the use of the first three digits is usually adequate. For example, B26 mumps, D22 melanocytic naevi, I95 hypotension, etc.

Hospital episode statistics (HES) data for England covering the years 2001/02 to 2008/09 at the level of three digit ICD code for primary diagnosis was obtained from the HESonline website (http://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=203). In general medicine the boundary between elective and emergency admission is far more ambiguous than for a surgical admission and hence trends in elective plus emergency overnight stay admission were studied, i.e. day case admissions were excluded. Exclusion of day case admissions is based on the fact that in medicine these are mainly diagnostic endoscopies or a range of outpatient procedures and tests which do not strictly meet the criteria as an inpatient [30-32]. In this instance an overnight stay hospital admission is taken to signify that the condition or disease was of sufficient severity that treatment in a secondary rather than primary care setting was required for recovery of the patient.

Diagnoses showing a statistically significant increase for both step-changes seen in the financial years 2002/03 versus 2003/04 and the 2007/08 versus 2008/09 were selected on the basis of a greater than a three standard deviation difference in the number of admissions between the paired years. In Poisson statistics a standard deviation is by definition equal to the

square root of the average and hence the square root of the number of admissions in the year before the step change is a good approximation to a standard deviation. This is then multiplied by three to define the size of a statistically significant change. The time trends for diagnoses meeting these criteria were then visually inspected to remove instances of change which were due to high background growth per se rather than a step change.
Having selected a group of diagnoses meeting this restrictive criteria they were added together to form a single group and the shape of the trend over time was determined. This general shape was then used to re-appraise the trends in admission for infectious and parasitic diseases (ICD Chapters A and B). Such diagnoses are usually characterised by relatively small numbers where it is difficult to demonstrate high statistical significance in the difference between one year and the next. Diagnoses which could possibly have the same shape for the trend over time were then selected by visual inspection and aggregated as before.

Results
After applying the restrictive criteria for a change in admissions of greater than three standard deviations for both the 2002 and 2007 step-changes a set of 86 primary diagnoses were identified. These were then subdivided into two groups. The first group contained only those diagnoses where the step change was clearly evident while the second group contained diagnoses where the change met the criteria but may have been less certain due to high background growth or unexpected volatility (see Tables 1& 2 and Fig. 1). A third group was constructed covering the infectious and parasitic diseases identified by the ICD chapters A and B. The selection of this group of diagnoses was aided by reference to the pattern of admissions over time shown in Fig 1 (see Table 3 and Fig. 2).

Discussion
Earlier studies on this topic have used the ICD summary level groupings of diagnoses in which some 1,655 potential diagnoses (at the three digit level) commonly used across England are clustered into 150 higher level groups [37-38]. At this point the issue of coding accuracy will usually be raised with assertions that poor coding is a confounding issue. While it is true that coding errors will occur and that systematic bias in the coding process occurs at all NHS sites it is not then true to assert that this will produce unique trends which are unrelated to the real nature of patient admission. This very issue was addressed in the editor's preface to the first systematic investigation into the annual and seasonal variation in the incidence of common diseases encountered in primary care [43]. It was argued that despite errors and ambiguity in diagnosis a set of clinically valid trends will still emerge and that these can then inform the direction of future research.
Hence within the medical group of specialties it had been suggested that something close to a perfect step change may be operating at an interval of between three to six years [3-7] and this is the rationale for searching for diagnoses which may mirror this pattern. It would appear that the transition from specialty down to individual diagnoses clarifies the nature of the trend. There appears to be an initial large step-change followed by future growth which declines over time. Such time-dependent behaviour could arise via higher rates of decease in susceptible members of the infected population, longer term recovery via the usual immune response or the transition to viral dormancy [44]. The key point is that there is a common pattern. This study is not claiming that the list of diagnoses in tables one to three is complete nor that some diagnoses may be later rejected but that there may be a common but unexpected linkage.
As has been previously proposed [37-38] the lists of diagnoses in Tables 1 to 3 do appear to contain conditions where a primary or secondary relationship to immune function could be implicated in the expression of necessary inpatient care. Immune function is the expression of an intricate and complex biological system. The literature contains numerous examples of

external factors which can either degrade or enhance the expression of immune function either temporarily or permanently [45-53]. Indeed a wide range of syndromes have been postulated to emanate out of immune system disfunction [54]. Hence what may be a disparate group of distinct diseases and conditions can therefore have underlying immune function as a common factor in the ultimate expression of chronic disease. On this occasion the three to six year pattern behind medical admissions could be said to be a 'Commonly infectious immune Function impairment' (CiiFi). Commonly infectious describes the three to six year cycle of infectious population outbreak while immune function impairment describes what appears to be the generally lower immune function which allows the chronic expression of underlying disease processes.

For example, the ultimate expression of tuberculosis (Table 3) is known to be associated with compromised immune function [55]. On this occasion the method has detected a common pattern of increasing hospital admission, i.e. for whatever reason the disease was severe enough to warrant inpatient rather than outpatient or primary care treatment. Of particular interest is the sub-group of nervous system disorders including convulsions, etc identified in Tables 1 & 2 which are known to sometimes manifest after viral infection [56-57] or dysregulation of the microglia which are the resident macrophages in the brain and spinal chord [58].

It is also of interest to note that the incidence of infectious and parasitic diseases appears to show a stronger cyclic pattern with a large increase in the step-year followed by declining growth for two years and then a fairly strong diminution of the cumulative effect.

The transition from Table 1 to Table 2 may represent conditions where the role of the immune system is of primary importance to one where the immune system is part of a number of factors leading to the expression of a hospital admission, i.e. the average value of the step change reduces and the shape of the trend over time is different.

The concept of looking for background patterns to identify infectious outbreaks is not new. Attendance at the emergency department, sales of analgesics and cough syrups, school absence, visits to general practitioners, etc have all been utilized to detect influenza and other infectious outbreaks [59-61]. What this study suggests is that far wider scale linkage between apparently un-associated diagnoses may be possible.

Further Studies

The need for inpatient care represents the tip of the spectrum of primary care activities. By implication the record-linkage data (where both acute and primary care records are linked) available to the NHS in Scotland would be an invaluable resource to further test the methodology and its conclusions. On this occasion a known phenomenon (i.e. an unexpected repeating step change) was used to inform the search for related diagnoses. The ultimate test is to see if the method can be expanded to find associations in the absence of an obvious reference point, i.e. the search for cause and effect in the case of appendicitis or other conditions.

The method needs to be further developed using pattern recognition or data mining software and expanding the available data from simple annual totals down to more powerful weekly or monthly views. Obviously Poisson-based statistical randomness begins to obscure the overall picture as the numbers get smaller but it is possible to aggregate the data in ways which overcome this limitation.

Conclusions

This study has both refined and broadened the list of diagnoses associated with the three to six year pattern in medical emergency admission seen in the UK. A pattern with a clear step may be associated with diagnoses with a primary linkage to immune function while a related but

less defined step-increase may involve conditions where immune function is one among other mechanisms for ultimate expression of the need for inpatient care.
Wider scanning of the entire range of diagnoses describing inpatient care may then detect common patterns between other conditions such as the particular types of appendicitis and so enable linkages that may not otherwise be readily apparent.
The wider linkage of the chronic expression of disease can then be used to inform healthcare policy and the potential search for infectious agents where immunisation will then prevent the expression of knock-on chronic disease.

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Table 1: Diagnoses where a clear step change has occurred.

ICD Code	Description	2003/04	2008/09	03/04 step	08/09 step
C48	Malignant neoplasm of retroperitoneum and peritoneum	1157	1526	24%	15%
D22	Melanocytic naevi	1464	1462	15%	22%
G43	Migraine	6954	11282	7%	16%
G45	Transient cerebral ischaemic attacks and related syndrome	16633	21185	6%	13%
G97	Postprocedural disorders of nervous system	445	797	21%	29%
H47	Other disorders of optic [2nd] nerve and visual pathway	448	581	23%	18%
H66	Suppurative and unspecified otitis media	6957	6627	7%	7%
I34	Nonrheumatic mitral valve disorders	2553	2908	10%	6%
I42	Cardiomyopathy	3445	3988	8%	8%
I51	Complications and ill-defined descriptions of heart disease	1547	2331	14%	40%
I63	Cerebral infarction	35770	44354	2%	6%
J06	Acute upper respiratory infections of multiple sites	45411	50348	13%	12%
J10	Influenza due to identified influenza virus	322	314	201%	140%
J11	Influenza virus not identified	950	673	42%	28%
J18	Pneumonia organism unspecified	88038	125601	9%	15%
J22	Unspecified acute lower respiratory infection	77965	91245	8%	13%
J40	Bronchitis not specified as acute or chronic	1265	1671	14%	11%
J44	Other chronic obstructive pulmonary disease	103917	109977	13%	10%
J45	Asthma	55875	61048	10%	11%
J84	Other interstitial pulmonary diseases	4960	5854	11%	6%
J86	Pyothorax	1910	2573	11%	11%
K59	Other functional intestinal disorders	34006	40602	6%	6%
M54	Dorsalgia	33679	48031	10%	8%
M62	Other disorders of muscle	2172	2520	10%	16%
N39	Other disorders of urinary system	82586	130444	10%	9%
O91	Infections of breast associated with childbirth	509	835	22%	16%
P08	Disorders related to long gestation and high birth weight	5332	8827	6%	10%
P28	Other respiratory conditions from the perinatal period	6612	8845	8%	9%
P36	Bacterial sepsis of newborn	1010	2310	15%	31%
R00	Abnormalities of heart beat	15496	21927	13%	8%
R06	Abnormalities of breathing	53006	76785	8%	14%
R07	Pain in throat and chest	181967	252091	9%	6%
R33	Retention of urine	25113	27183	3%	4%
R42	Dizziness and giddiness	12787	19252	12%	11%
R50	Fever of unknown origin	15134	22455	13%	5%
R53	Malaise and fatigue	10415	14632	11%	13%
R55	Syncope and collapse	64032	91643	10%	9%
R56	Convulsions not elsewhere classified	35375	41528	9%	5%
R68	Other general symptoms and signs	3023	5559	13%	65%
R69	Unknown and unspecified causes of morbidity	229695	116827	19%	10%
T42	Poisoning by antiepileptic, etc drugs	12608	15435	11%	5%
Z04	Examination and observation for other reasons	10334	15273	41%	57%
	Total	**1292877**	**1509349**	**11%**	**10%**

Table 2: Diagnoses where the step change may be mixed with other factors.

ICD Code	Description	2003/04	2008/09	03/04 step	08/09 step
B34	Viral infection of unspecified site	39,911	48,619	4%	12%
E11	Non-insulin-dependent diabetes mellitus	13,669	17,615	7%	8%
E16	Other disorders of pancreatic internal secretion	7,596	12,900	6%	12%
E66	Obesity	1,212	5,287	29%	47%
E87	Other disorders of fluid, electrolyte and acid-base balance	8,521	15,614	19%	15%
F10	Mental and behavioural disorders due to use of alcohol	31,565	42,995	10%	3%
G44	Other headache syndromes	2,260	3,178	9%	10%
G51	Facial nerve disorders	2,478	3,993	7%	13%
H35	Other retinal disorders	3,064	4,113	12%	11%
H53	Visual disturbances	2,641	4,275	11%	16%
I48	Atrial fibrillation and flutter	55,910	68,088	6%	2%
I95	Hypotension	8,387	13,635	13%	10%
J00	Acute nasopharyngitis [common cold]	773	1,628	13%	29%
J47	Bronchiectasis	5,203	6,430	11%	7%
J98	Other respiratory disorders	4,621	5,500	6%	11%
K04	Diseases of pulp and periapical tissues	3,974	5,278	8%	5%
K57	Diverticular disease of intestine	20,702	22,161	3%	3%
K85	Acute pancreatitis	13,879	17,160	6%	5%
K92	Other diseases of digestive system	35,839	42,534	3%	6%
L02	Cutaneous abscess, furuncle and carbuncle	23,199	28,571	9%	6%
L03	Cellulitis	48,889	56,232	10%	4%
M15	Polyarthrosis	2,772	7,215	19%	36%
M25	Other joint disordersnot elsewhere classified	30,681	50,866	6%	21%
M79	Other soft tissue disorders not elsewhere classified	46,936	66,176	4%	10%
N12	Tubulo-interstitial nephritis	6,405	10,045	11%	14%
N20	Calculus of kidney and ureter	21,890	30,502	11%	8%
O90	Complications of the puerperium	3,961	6,323	16%	5%
P20	Intrauterine hypoxia	23,144	25,084	6%	3%
P92	Feeding problems of newborn	7,387	12,478	7%	10%
R10	Abdominal and pelvic pain	181,762	227,143	6%	3%
R18	Ascites	4,854	8,403	13%	9%
R20	Disturbances of skin sensation	3,621	6,603	10%	17%
R25	Abnormal involuntary movements	2,873	4,125	8%	8%
R26	Abnormalities of gait and mobility	7,198	6,954	5%	10%
R31	Unspecified haematuria	15,736	20,379	6%	6%
R41	Symptoms and signs of cognitive function & awareness	18,341	27,112	12%	13%
R47	Speech disturbances, not elsewhere classified	2,357	5,191	11%	24%
R51	Headache	32,540	50,753	9%	9%
R54	Senility	27,665	42,175	8%	16%
R79	Other abnormal findings of blood chemistry	1,710	5,460	25%	15%
T40	Poisoning by narcotics and hallucinogens	6,545	9,954	12%	4%
T83	Complications of genitourinary prosthetic devices & grafts	6,825	11,279	5%	13%
Z27	Immunization against combinations of infectious diseases	646	333	24%	24%
Z45	Adjustment and management of implanted device	6,765	8,467	5%	9%
	Total	**796,907**	**1,068,826**	**7%**	**8%**

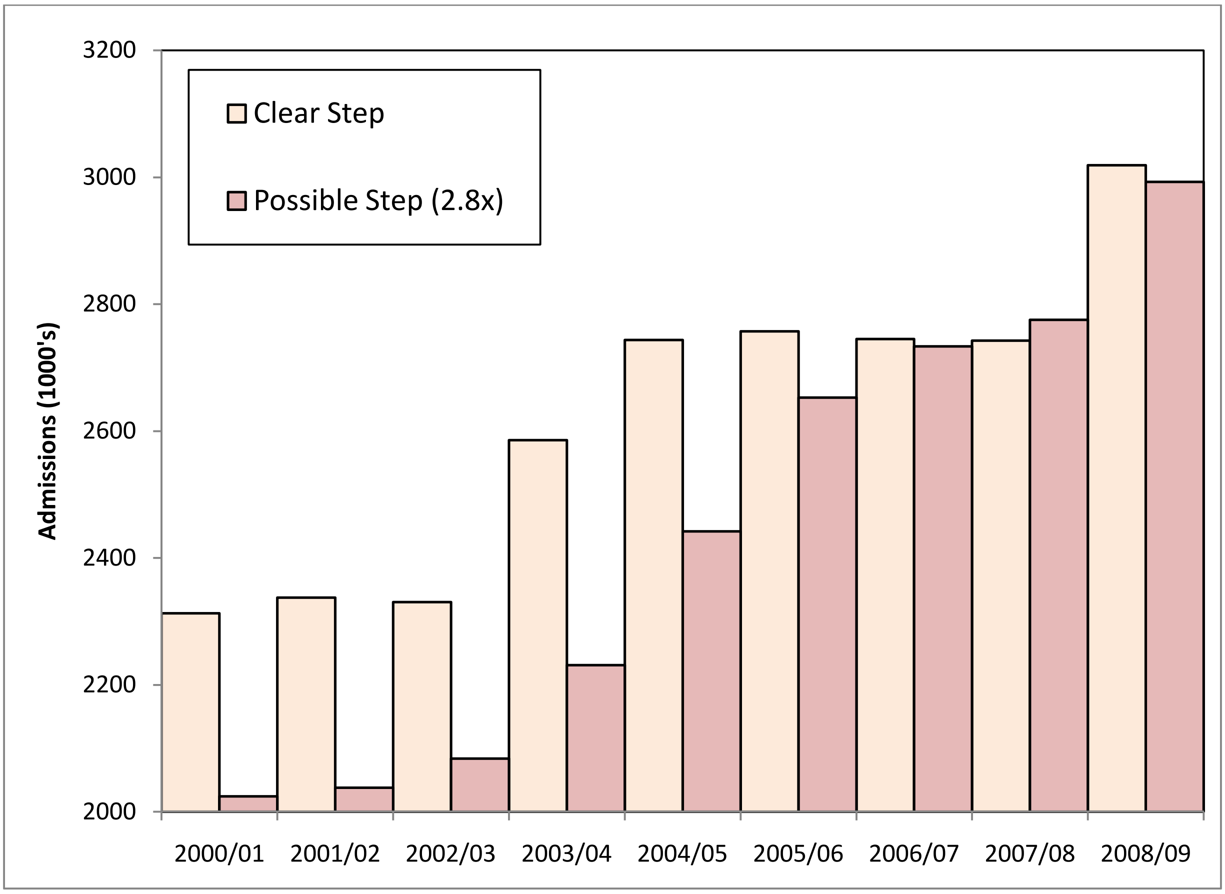
Footnote: Diagnoses such as R79, M15, R47, J00, etc showing high apparent growth between 2003/04 and 2008/09 may have additional confounding effects due to increases in zero day stay 'admissions'.

Table 3: Diagnoses related to infectious and parasitic diseases.

ICD	Description	2002/03	2003/04	2007/08	2008/09
A01	Typhoid and paratyphoid fevers	169	247	351	367
A03	Shigellosis	61	68	76	87
A07	Other protozoal intestinal diseases	165	239	160	212
A20	Plague	2	2	0	3
A25	Rat-bite fevers	3	6	1	2
A30	Leprosy [Hansen's disease]	12	21	3	4
A32	Listeriosis	33	63	64	58
A35	Other tetanus	15	22	21	21
A38	Scarlet fever	250	259	294	421
A39	Meningococcal infection	2075	2033	1593	1607
A40	Streptococcal septicaemia	979	1060	1110	1213
A43	Nocardiosis	2	9	1	8
A46	Erysipelas	310	354	265	281
A50	Congenital syphilis	7	10	8	15
A52	Late syphilis	72	93	92	99
A53	Other and unspecified syphilis	20	29	22	26
A68	Relapsing fevers	2	6	5	8
B95	Streptococcus and staphylococcus	62	68	11	26
B96	Other bacterial agents	54	51	27	39
B97	Viral agents	85	45	13	46
B09	Viral infection with skin & mucous membrane lesions	373	415	571	679
B05	Measles	77	108	353	409
B56	African trypanosomiasis	1	9	9	12
B57	Chagas' disease	0	20	0	0
B37	Candidiasis	1345	1489	1697	1745
B33	Other viral diseases, NEC	114	182	98	117
B36	Other superficial mycoses	35	44	37	65
B87	Myiasis	4	6	11	15
B43	Chromomycosis and phaeomycotic abscess	1	3	4	10
B90	Sequelae of tuberculosis	2	5	0	1
B91	Sequelae of poliomyelitis	3	9	0	3
B76	Hookworm diseases	7	12	2	7
B19	Unspecified viral hepatitis	180	230	195	215
B20	HIV disease resulting in infectious parasitic diseases	961	1040	1471	1627
B26	Mumps	96	143	198	281
	Total	**7577**	**8400**	**8763**	**9729**

Footnote: The diagnosis B34 (viral infection of unspecified site) is listed in Table 2.

Fig. 1: Time-trends related to the clusters of diagnoses in tables 1 and 2.



Footnote: Apparent growth subsequent to 2003/04 in the 'Possible Step' group may be partly due to increases in zero day stay 'admissions' for particular diagnoses.

Fig. 2: Time-trend related to the cluster of diagnoses in table 3.