27 September 2013

IMEG Report on Infectious diseases and sequelae in recent deployed service

1. Following several claims for deployment related febrile illness and their sequelae, IMEG was asked by Minister to investigate and report on the AFCS approach to these disorders, with a particular focus on Q fever and post Q fever fatigue syndrome (QFS).This short report was informed by literature search and discussion with relevant military and civilian experts.

2. Despite a significant body of published scientific and medical literature on fatiguing illness, there remain many uncertainties and gaps in the evidence, particularly on post –infective fatiguing illness and QFS. While a Dutch group has recently published a protocol for a prospective cohort study on the health impact of Q fever up to four years from clinical onset of the acute illness (1) there is currently no planned cohort study with follow-up beyond about 26 months (2). These evidential limitations constrain IMEG's findings and recommendations.

Deployed service and infectious disease

3. Undifferentiated febrile illnesses (known as "Helmand Fever" when occurring in Afghanistan) meningitis, encephalitis and gastroenteritis seem to be the commonest infectious causes of long-term symptoms following deployments. Today, most deployment-related febrile illness is self-limiting, lasting at most a few weeks with a low rate of morbidity and mortality in the acute phase. In 2008 a small study identified 26 cases of "Helmand Fever " diagnosed clinically over six months and, to identify cause, applied a standard protocol including acute and convalescent serology

(3). In about 10% of cases no firm diagnosis was made. 52% of the remaining cases were viral due to sand fly fever; 22% due to rickettsial infections, commonly typhus, and 26% were bacterial due to Q fever. Of these, only Q fever is associated with significant disabling illness and sequelae.

Q fever

4. Q fever was first described in Queensland, Australia in 1937. Notable outbreaks have since occurred in Birmingham in 1989 and in Holland in 2007-2010. It is a zoonosis caused by Coxiella burnetii infection, transmitted especially from parturient animals. It is highly infectious and spread by inhalation from wind borne spores (4). Q fever occurs around the world with slightly different clinical symptoms and patterns. The Public Health Laboratory Service confirms about 100 sporadic cases per annum in the UK.

5. In the current Afghanistan deployment 3.4% of troops have serological evidence of new Coxiella burnetii infection each year with about half (-340 per year) being asymptomatic or with very mild symptoms. The other half have a flu like illness with fever, myalgia, arthralgia, tiredness or atypical pneumonia. The acute phase is not usually life threatening and most cases make a good recovery in a few weeks. Up to a quarter have varying degrees of persisting fatigue and functional limitation - post Q fever fatigue syndrome (QFS). This occurs most commonly where fatigue is a prominent symptom at the beginning of the illness. These may be accompanied by muscle pain with fasciculation and night sweats. About 16% of military cases of acute Q fever will be unable to pass a military fitness test at a year after the acute illness. Chronic Q fever, a discrete entity, diagnosed serologically, is generally thought to

affect about 1-5% of those infected and usually presents as endocarditis. No military cases have yet been confirmed from Afghanistan. In Australia, where the disorder is especially troublesome amongst stockmen and abattoir workers a Q fever vaccination programme was introduced in 2001. No vaccine is yet licensed for use in the UK. UK military clinical management of Q fever includes empirical use of doxycycline for two weeks. Clinically this seems to reduce the severity of the acute illness and to lower the risk of QFS. In different Q fever outbreaks there are core symptoms/features with variations. Most reported outbreaks include patients with fatigue during both the acute illness and longer term. While variation in bacterial strain may be relevant, there is at present no clear explanation for the different clinical patterns. It is also unclear whether persistent fatigue in QFS is a long term manifestation of Q fever or a specific consequential disorder.

6. In the 1989 Birmingham Q fever outbreak, 147 cases occurred in a month, with the infection source being birth by-products from ewes lambing in the fields south of the M42. Spores were spread due to unusual weather conditions with, on one April day, southerly gales up to 80 mph. The acute disease was severe, often requiring hospitalization. Symptoms included dramatic weight loss, up to one stone in a week. Chest symptoms were prominent, with a range of radiographic change including lobar pneumonia. Neurological symptoms were also common, including headache and visual problems. At six month follow-up, a third of patients were still symptomatic and complaining of fatigue. Of the 147 cases seen in the acute phase, two had myocarditis and two later developed chronic Q fever with endocarditis (5).

7. Five years after the Birmingham outbreak, amid evidence of continuing

poor health, 142 of the original 147 patients were traced and asked to complete a postal questionnaire. The controls were age, sex and geographical location matched persons, who had not complained of symptoms during the outbreak. The study looked at 71 patients and 142 matched controls. Symptoms such as fatigue, sweating, breathlessness, blurring of vision were more common in cases than controls although there was also a significant symptom rate in the controls. No serology was available for the controls, so it is possible that they may have included some mild or asymptomatic cases of Q fever (6).

8. Further follow-up of this cohort at ten years post-infection included hospital interview, clinical examination and a standard battery of tests including serology. Controls matched for age, sex and smoking were selected from GP lists. The protocol included the administration of the Wessely Chalder fatigue instrument and psychological symptoms were covered by GHQ psychometric measure. Again fatigue symptoms were more common in cases than controls and similarly GHQ case criteria were met in 47% of cases and 23% controls (7). 10% of cases had QFS (using the above criteria). It should be appreciated that the infected population was not age or gender limited as is the case with the military population and the average age at the time of infection was in the forties in this outbreak.

9. Between 2007 and 2010 the Netherlands had the largest outbreak of Q fever yet reported, with 4000 cases and an estimated 44000 infected (8). Study of the Dutch patients show that, as with the Birmingham outbreak, following acute Q fever 10-15%

still had disabling symptoms, most commonly QFS, present 12 – 26 months after initial infection (2).

.

10. Other infectious agents relevant to military populations associated with post-infectious fatigue include infectious mononucleosis, viral hepatitis, viral meningitis, parvovirus and non-viral agents including Lyme disease. In post-infective fatigue states in addition to generic symptoms, specific infections can be associated with particular symptoms such as nausea and fatty food intolerance in hepatitis and sore throat and painful cervical lymphadenopathy in infectious mononucleosis. Research findings suggest that some 10-13% of cases of these infections go on to develop post infective fatiguing state (9). Factors which have been suggested to increase risk include:

i) pre-morbid fatigue and depression.

ii) very severe initial infection.

iii) the patient's belief that the illness will be prolonged with difficult recovery so he needs to rest.

iv) resultant physical deconditioning.

In addition there may be possible links to:

v) abnormal autonomic nervous system function e.g. low heart rate beat to beat variability.

vi) down-regulation of the hypothalamic-pituitary-adrenal axis (low cortisol may be a factor in some types of CFS but has not been shown in post infective states).

vii) immune abnormality (findings in post-infective fatigue states are inconsistent).

viii) host genetic factors.

Are post infective fatiguing illnesses including QFS the same disorder as chronic fatigue of spontaneous onset?

11. Cases with QFS usually meet the general case definition for spontaneous Chronic Fatigue Syndrome (CFS) (10). However, information on the natural course, average duration and prognosis of QFS, whether treated or untreated, is sparse. It is also unknown whether chronic fatigue following infection is the same entity or different from CFS of spontaneous onset.

12. In most studies of chronic fatiguing illness of spontaneous onset the great majority of patients are women. In contrast, while the UK Afghanistan military and Australian abattoir studies of QFS are occupationally based, with predictably men mainly affected, there was also a clear preponderance of working age men in the Birmingham outbreak where no links to occupation were identified. Three quarters of those affected were employed working aged males. Just one child was infected and only three non-white people. CFS is usually a diagnosis of exclusion. Of patients referred to secondary care CFS Clinics, with six months or more of abnormal fatigue, poor concentration and sleep, myalgia and arthralgia of unknown aetiology, about half do not have CFS but other diagnoses such as depression. CFS is often associated with other somatic disorders such as fibromyalgia, migraine, irritable bowel syndrome, or functional somatic syndromes. These associations are considerably less common with post infectious fatigue syndrome. Some patients with spontaneous CFS also have discrete psychological disorders, but again there is no evidence that post infective fatigue states are particularly associated with specific psychological diagnoses.

13. Although, as referenced above, overall study numbers are small and results inconsistent and difficult to interpret in terms of causation or consequence, a number of studies on the mechanism of fatiguing illness suggest that post infectious CFS may be quite different from spontaneous onset CFS (11). Studies from Australia and Birmingham show that in QFS, persistent symptoms are associated with either antigen or organism retained in tissues, notably the bone marrow of these patients (12). Potential immunological mechanisms and host genetic influences are emerging research topics which may in the future provide improved understanding of the core features of infectious disorders and of pre-disposing or precipitating factors of post-acute phase fatigue (13).

Prognosis of fatiguing illness

14. A variety of treatments ranging from steroids to anti-infective treatment has been provided for fatiguing illness following infection. In general, for all types of persistent fatigue state, optimal management is based on: i) accurate diagnosis of all disorders including co-morbid sleep problems, depression and pain; ii) treatment of co-morbid conditions; iii) focus on the fatiguing illness with active rehabilitation. Research findings show that individually (not group) delivered Cognitive Behavioural Therapy (CBT) and Graded Exercise Therapy (GET) as compared to specialist medical care alone are moderately effective (effect sizes 0.5 to 0.8) when added to specialist medical care and delivered in courses of suitable intensity and duration by well qualified and trained therapists (14).

15. The published literature on the natural course, duration, prognosis and effective interventions for fatiguing illness of all types is limited. Disability, functional outcomes and employability have not been a major focus of studies and comparison of studies and interpretation is hindered by different case definitions and whether patients are drawn from primary or specialist care settings, the latter usually being the more severe cases. The prognosis for patients receiving specialist care for persisting fatiguing illness (spontaneous and post infective) without specific treatment is poor. A 2005 meta-analysis of 14 studies, of sample sizes between 20 to 3201, with defined entry criteria, published between 1991 and 2002 and followed for between 5 and 10 years showed untreated, a median full recovery rate of 5% (with a range across the studies of 0-31%) while there was symptomatic improvement at follow-up in a median of 39.5% cases (range 8-63%). Better outcomes were associated with less severe fatigue at the onset, patients having a sense of control over symptoms and not attributing illness to a physical cause (15).

AFCS approach to infections and their sequelae

16. The armed forces population is on average young, male and fitter than the age and sex matched civilian equivalent and claims for physical disorders are unusual. It was anticipated that infections might be an issue for the Scheme and the legislation sets out the circumstances, where benefit may be payable for an exogenous infection. These are first deployed service and, in a temperate region, where there has been an outbreak of the infection in service accommodation /workplace.

Table 4 – Physical disorders including infectious diseases*

Column (a) Level	Column (b) Injury
6	Physical disorder causing severe functional limitation and restriction where life expectancy is less than five years.
7	Physical disorder causing severe functional limitation and restriction where life expectancy is reduced, but is more than 5 years.
9	Physical disorder causing permanent severe functional limitation and restriction.
11	Physical disorder which has caused, or is expected to cause severe functional limitation and restriction at 26 weeks where the claimant has made, or is expected to make, a substantial recovery beyond that date.
11	Physical disorder causing permanent moderate functional limitation and restriction.
12	Permanent physical disorder where symptoms and functional effects are well controlled by regular medication.
13	Physical disorder which has caused, or is expected to cause, moderate functional limitation and restriction at 26 weeks, from which the claimant has made, or is expected to make, a substantial recovery beyond that date.
14	Physical disorder which has caused, or is expected to cause, severe functional limitation and restriction at 6 weeks, from which the claimant has made, or is expected to make, a substantial recovery within 13 weeks.
14	Physical disorder which has caused, or is expected to cause, moderate functional limitation and restriction at 13 weeks, from which the claimant has made, or is expected to make, a substantial recovery within 26 weeks.
15	Physical disorder which has caused, or is expected to cause, moderate functional limitation and restriction at 6 weeks, from which the claimant has made, or is expected to make, a substantial recovery within 13 weeks.

*Any reference to duration of effects in column (b) is from date of injury or onset of illness.

*Awards for injuries in this table include compensation for any associated psychological effects short of a distinct diagnosable disorder.

17. AFCS descriptors assess severity of injuries and disorders in terms of the associated functional restriction or limitation and their duration. When choosing a descriptor it is useful to consider first the likely impact of the accepted condition on civilian employability , whether or not a Guaranteed Income Payment (GIP) is appropriate, and at what level. This allows narrowing of tariff range and finally individual tariff selection. Awards should be consistent providing horizontal equity i.e. across the range of disorders and Tariff tables, and vertical equity i.e. across the degrees of severity of an injury /disorder category in a single Table. To provide financial certainty for claimants when they leave service, the Scheme aims to make full and final awards as early as possible. Ideally this is when the injury or disorder is in a steady state of maximum medical improvement, following an adequate course of best practice treatment. When the disorder is not in a steady state, an interim award may be paid for up to four years post initial notification. Functional limitation or restriction is considered permanent where an injury has reached a steady state of maximum medical improvement with no further improvement expected.

18. Tables 3 and 4 of the Tariff relate to Mental Disorders and Physical Disorders – including infectious diseases. The Tables do not list specific diagnoses but are generic. Table 3 has previously been reviewed by IMEG and Table 4 descriptors and Tariff levels were informed by civil awards where currently (2013) a highly malignant life-limiting disease such as mesothelioma would attract a general damages award of about £100,000. This compares with AFCS Tariff level 8 which is £60,000; Level 7 £90,000 and level 6, £140,000. Items 1 and 2 of Table 4 apply to disorders with

reduced life expectancy, not an issue with post –infective fatiguing illness. Where Table 4 items 1 and 2 are paid, death and dependents' benefits will also apply. For both Tables 3 and 4 the highest GIP band is Band B based on 75% service salary at service termination. Injuries attracting AFCS band A i.e. 100% salary base ,include full thickness burns affecting 70% or more body area; several categories of severe polytrauma and amputations; severe brain and spinal injuries and loss of senses. The descriptors aim to reflect injuries and disorders relevant to the military population and potentially attributable to AFCS service. The most severe and enduring mental health disorders in terms of very severe functional compromise and employability are the psychotic disorders which, in line with contemporary medical understanding are not on balance of probabilities due to AFCS service.

19. As discussed, for post infective fatiguing illness of all types, including QFS, there remain many uncertainties, which include best practice treatment and prognosis. End points and outcomes used in the few published studies are variable, often expressed as self-reported symptoms, not using an objective functional measure and, there has been no reported planned prospective study providing reliable evidence on time course or prognosis, although the proposed Dutch cohort study may provide this in the future. The available evidence indicates that a minority of people do recover, sometimes years after onset and apparently spontaneously, treated or untreated.

Suggested descriptors for Q fever and QFS.

20. Current Table 4 descriptors do not well reflect the range of QFS functional limitation or restriction and the following additions are suggested:

- Physical disorder causing permanent very severe functional limitation or restriction level 6
- Physical disorder causing permanent severe functional limitation or restriction level 8

The existing item 5 level 11 should remain

- Physical disorder causing permanent moderate functional limitation or restriction level 11

In the footnote to Table 4 in respect of physical disorders

“very severe” Permanent functional limitation or restriction is very severe when the claimant is unable to undertake work appropriate to experience, qualifications and skills, following best practice treatment and at best thereafter is able only to undertake work sporadically and in physically undemanding jobs.

“severe” Permanent functional limitation or restriction is severe where the claimant is unable to undertake work appropriate to experience, qualifications or skills at the time of onset of the disorder and over time able to work only in physically less demanding jobs.

”moderate” Permanent functional limitation or restriction is moderate where the claimant is unable to undertake work appropriate to qualifications skills and experience at the time of onset of the illness but in time able to work regularly in a less physically demanding job.

To maintain coherence the Table 4 descriptors and definitions have a similar format to those in Table 3 , Mental disorders. Awards for Physical disorders include psychological symptoms but do not include primary cognitive, mood or behavioural symptoms and are generally paid lower awards than equivalent mental disorders. Factors taken into account in valuing awards for mental disorders include the associated vulnerability and compromised relationships with family, friends and at work. The descriptors proposed above for Q fever and its sequelae will also apply to other infections and primary physical disorders and their sequelae.

20 September 2013

References:

(1) van Loenhout, J.A.F et al Assessing the long-term health impact of Q -fever in the Netherlands: a prospective cohort study started in 2007 on the largest documented Q –fever outbreak to date BMC Infectious Diseases (2012); 12:280

(2)Morroy, G. et al The health status of Q-fever patients after long-term follow-up BMC Infectious Diseases (2011);11: 97

(3) Bailey, M.S. et al Undifferentiated febrile illnesses amongst British troops in Helmand, Afghanistan JR Army Med Corps (2011);157;150-155

(4) Parke, N.R. et al Q fever Lancet (2006); 367: 679-688

(5) Smith, D.L. et al A large Q fever outbreak in the West Midlands ; clinical aspects Resp Med (1993); 87: 509-516

(6) Ayres, J.G. et al Post infection fatigue syndrome following acute Q fever: follow-up study of patients involved in the 1989 outbreak in the West Midlands Q J Med (1998); 91:105-123

(7) Ayres,J.G. et al Long term follow-up of patients from the 1989 fever outbreak no evidence of excess cardiac disease in those with fatigue . Q J Med (2002);95:539-46

(8) Roest, H .I. J. et al The Q fever epidemic in the Netherlands: history onset, response and reflection Epidemiol. Infec (2011) 139:1-12

(9) Hickie,I.et al Post-infective and chronic fatigue syndromes precipitated by viral and non –viral pathogens: prospective cohort study .BMJ,doi:10.1136/bmj.38933.5875764.AE

(10) Fukuda,K. et al The chronic fatigue syndrome : a comprehensive approach to its definition and study Ann Int Med (1994) 121:953-59

(11) Wilson,A et al What is chronic fatigue syndrome? Heterogeneity within an international multicentre study . Aust NZ J Psych (2001) 35: 520-7

(12) Marmion,B.P.et al Long term persistence of Coxiella burnetii after acute primary Q fever. Q J Med (2005) ;98:7-20

(13) Pentilla,I.A . et al Cytokine dysregulation in the post –Q –fever fatigue syndrome Q J Med (1998) 91:549-560

(14)_ White, P.D. et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. The Lancet 2011;377:823-36.

(15) Cairns, R. et al A systematic review describing the prognosis of chronic fatigue syndrome Occup Med (2005) ;55: 20- 31