Plenty of inflammatory syndromes implicated in Long COVID but are there others?

- **A syndrome is defined as a set of medical signs and symptoms** which are correlated with each other and often associated with a particular disease or disorder. **A syndrome tells us nothing about its cause, merely its components.**
- There are several **other suggested syndromes. But how useful are they?**
- Many researchers have hypothesised that Long COVID might reflect various syndromes, although the range of symptoms of Long COVID suggests that it may be broader than those of any other defined syndrome.
- Others have suggested that patients may be suffering with more than one syndrome.
- Even more tried to suggest that Long COVID is not 1 single condition but can be categorised into several conditions or have subtypes. The Zoe App study divided long COVID symptoms into 2 types:
    1. People reporting exclusively fatigue, headache and upper respiratory complaints (shortness of breath, sore throat, persistent cough and loss of smell) and
    2. Those with additional multi-system complaints, including ongoing fever and gastroenterological symptoms.

(https://evidence.nihr.ac.uk/themedreview/living-with-covid19-second-review/; https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/alldatarelatingtoprevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk; https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/resource/en/ppmedrxiv-20208702; Sudre, C.H. et al. Attributes and predictors of long COVID. Nat Med, 2021, 27, 626–631; Mahase E, Long covid could be four different syndromes, review suggests. BMJ 2020; 371: m3981)

All these syndromes have been suggested as mechanisms in the causation of Long COVID

- Post-viral syndrome
- Post-intensive care syndrome
- Multisystem inflammatory syndrome – children (MIS-C) – see earlier lecture

- Multisystem inflammatory syndrome – adults (MIS-A) – see earlier lecture
- Systemic inflammatory response syndrome (SIRS) – see earlier lecture
- Chronic Inflammatory Response Syndrome (CIRS) – see earlier lecture
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- Chronic fatigue syndrome (CFS)
- Postural orthostatic tachycardia syndrome (POTS)
- Macrophage activation syndrome

Post-viral syndrome

- **Interestingly, a PubMed search revealed no article since 1987 with 'Post-viral syndrome' in the title, other than in relation to COVID-19!**
- A 1987 review article: Post-viral syndrome 'typically follows an upper respiratory tract infection from which the sufferer fails to make a full recovery, complaining of a multitude of symptoms which may persist for months or even years. The cardinal symptom is profound muscular fatigue and this is often accompanied by muscle pain, headache, paresthaesia, dizziness, urinary frequency, cold extremities, bouts of sweating and fainting attacks. Other symptoms are poor memory, lack of concentration, sleep disturbance, mild expressive and receptive dysphasia, hyperacusis and emotional lability. Clinical examination usually shows no abnormalities, nor do routine laboratory investigations. The diagnosis is therefore one of exclusion.'
- It goes on to say: 'Doubt has been cast on the organic nature of the disease. Hysteria may account for many of the cases'. (Archer MI. The post-viral syndrome: a review. J R Coll Gen Pract. 1987 May;37(298):212-4)
- However, it is still referred to in popular health websites, which normally emphasise fatigue as the principal symptom (https://www.medicalnewstoday.com/articles/326619).

The concept of post-viral syndrome is not new

- In 1892, Josephine Butler, the English women's right campaigner, wrote to her son complaining of unresolved fatigue after being infected with the Russian Influenza.
- The Russian flu also affected many politicians in the UK, including the prime minister. In 1895 several reflected in their periodicals and diaries about the long-lasting fatigue and insomnia.

(Honigsbaum M, Krishnan L. Taking pandemic sequelae seriously: from the Russian influenza to COVID-19 long-haulers. Lancet. 2020 Oct 31;396(10260):1389-1391)

Even Fauci acknowledges that post–viral syndrome may be involved in Long COVID

- "**Brain fog, fatigue, and difficulty in concentrating….this is something we really need to seriously look at because it very well might be a post-viral syndrome associated with COVID-19**." (Dr. Fauci, speech at International AIDS Conference)
- Interestingly, he also said that COVID-19 "should be very helpful now in getting us to be able to understand [ME/CFS]".

(https://www.ctvnews.ca/health/coronavirus/some-covid-19-long-haulers-are-developing-a-devastating-syndrome-1.5415288)

Post-intensive care syndrome (PICS)

- This is characterised by chronically impaired pulmonary function, neuromuscular weakness, long-term psychological impact and reduced quality of life. It is common among people with severe acute infections who have spent long periods on ventilators.
- Factors which may be directly related to mechanical ventilation include risks of lung damage, secondary infection and pulmonary fungal infections. In addition, the prolonged immobility and metabolic changes can play a role in inducing symptoms. (Desai SV, et al. Long-term complications of critical care. Crit Care Med. 2011 Feb;39(2):371-9)
- Among patients who had been discharged after intensive care unit stay, where 46% required mechanical ventilation, 84% reported impairment in cognition, mental health or physical function that persisted for 6-12 months. (Maley JH, et al. Resilience in survivors of critical illness in the context of the survivors' experience and recovery. Ann Am Thorac Soc. 2016;13(8):1351-1360)
- Other studies report similar results, including deconditioning, particularly after mechanical ventilation (Inoue S, Hatakeyama J, Kondo Y, et al. Post-intensive care syndrome: its pathophysiology, prevention, and future directions. Acute Med Surg. 2019;6(3):233–246; Rawal G, Yadav S, Kumar R. Post-intensive Care Syndrome: an Overview. J Transl Int Med. 2017;5(2):90–92; Raveendran AV. Long COVID-19: Challenges in the diagnosis and proposed diagnostic criteria. Diabetes Metab Syndr. 2021 Jan-Feb;15(1):145-146; https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/publications-and-technical-guidance/2021/in-the-wake-of-the-pandemic-preparing-for-long-covid-2021)

Chronic Inflammatory Response Syndrome (CIRS)

- Chronic Inflammatory Response Syndrome (CIRS) is a progressive, multi-system, multi-symptom illness characterized by **exposure to biotoxins**. The ongoing inflammation can affect virtually any organ system of the body and if left untreated becomes debilitating.
- CIRS is an activation of the innate immune system, making a proper diagnosis difficult since common parameters of inflammation are generally negative upon laboratory evaluation. CIRS is a brain on fire, a dominant clinical feature being the common cognitive complaints by patients, including memory loss, mood disorders, brain fog, loss of executive function and fatigue. This is not a surprise considering that this is a key component of the innate immune response. There are multiple markers to measure the innate response and measure the presence of inflammation in the brain.
- Chronic Inflammatory Response Syndrome (CIRS), also known as biotoxin illness, describes a group of symptoms, lab findings, and targeted test results associated with biotoxin exposure, especially in genetically-susceptible people.
- The term was first coined by Dr. Ritchie Shoemaker to describe the results of exposure to toxin-producing organisms and water-damaged buildings.

(https://www.vc4hw.com/chronic-inflammatory-response-syndrome-cirs.html; https://www.survivingmold.com/)

Central sensitisation syndrome (CSS)

- Central sensitisation syndrome is a group of conditions including chronic headache, irritable bowel syndrome and fibromyalgia. They are believed to have shared physiological processes with brain inflammation and changing of the brain and spinal cord pathways, with an increase in cytokine and chemokine levels. In all cases, there are increased IL-6 levels >3 months after infection, which is associated with fatigue and sleep disturbance. Treatment of these symptoms has usually been frustrating, as patients have several such disabling symptoms but almost no abnormalities in lab tests. (Bierle DM, et al. Central Sensitization Phenotypes in Post Acute Sequelae of SARS-CoV-2 Infection (PASC): Defining the Post COVID Syndrome. J Prim Care Community Health. 2021 Jan-Dec;12:21501327211030826)
- A study comparing surveys completed by patients found that there were symptoms of central sensitisation in more than 70% of Long COVID patients. (Goudman L, et al. Is Central Sensitisation the Missing Link of Persisting Symptoms after COVID-19 Infection? J Clin Med. 2021 Nov 28;10(23):5594)
- Central sensitisation encompasses many disorders where the central nervous system amplifies sensory input across many organ systems and results in myriad symptoms. There is substantial overlap among the case definitions and diagnostic criteria for these disorders, even for core symptoms. (Fleming KC, Volcheck MM. Central sensitization syndrome and the initial evaluation of a patient with fibromyalgia: a review. Rambam Maimonides medical journal vol. 6,2 e0020. 29 Apr. 2015, doi:10.5041/RMMJ.10204)

Mast Cell Activation Syndrome (MCAS)

- Mast Cell Activation Syndrome (MCAS) is a multisystem, inflammatory disease caused by mast cell hyperactivity and release of inflammatory cytokines. MCAS is a disorder where mast cells may be normal in number, but release excessive amounts of mast cell mediators, such as histamine, in response to dietary or environmental triggers. The symptoms of MCAS can be very similar to that of CFS/ME and therefore may be confused. Excess histamine can cause severe inflammation and a wide variety of symptoms. Almost any organ system in the body can be affected by MCAS. Most patients experience fatigue, fevers and sensitivity to individualised environmental "triggers“, as well as a range of other symptoms. Because a variety of symptoms can be present, MCAS is commonly misdiagnosed. (L.B. Afrin, et al, Characterization of mast cell activation syndrome, Am J Med Sci 353 (3) (Mar 2017) 207–215; https://me-pedia.org/wiki/Mast_cell_activation_syndrome)
- Symptoms experienced in MCAS largely overlap with those seen in Long COVID, including chest pain, palpitations, and dyspnoea. Some have theorized that prolonged COVID-19 symptomatology may be due to abnormal hyperactivation of mast cells in patients with underlying primary MCAS. Much of Covid-19's hyperinflammation is concordant with inflammation driven by dysfunctional mast cells. (L.B. Afrin, et al, Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome, Int. J. Infect. Dis. 100 (Nov 2020) 327–332)
- Researchers have proposed that MCAS may also underlie long COVID pathophysiology. Mast cells serve as a fibroblast-activating factor that could lead to pulmonary fibrosis seen in long COVID sufferers. Indeed, SARS-CoV-2 has been shown to trigger inflammatory mast cell responses alongside other immune cells in COVID-19 patients. (Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. Infect Dis (Lond). 2021 Oct;53(10):737-754)
- Patients with Long COVID following a mild COVID-19 infection had reduced CD4+ and CD8+ effector memory (EM) cell numbers and increased PD-1 (programmed cell death protein 1) expression on central memory (CM) cells persisting for several months. 72% of patients with long COVID who received histamine receptor antagonists (HRAs) reported clinical improvement, suggesting MCAS, although T cell profiling did not clearly distinguish those who responded to HRA. (Glynne P, et al. Long COVID following mild SARS-CoV-2 infection: characteristic T cell alterations and response to antihistamines. J Investig Med. 2022 Jan;70(1):61-67)

Chronic fatigue syndrome (CFS) – it's not just about fatigue

According to the NHS, chronic fatigue syndrome (CFS) may also be called myalgic encephalomyelitis (ME). It is a is a long-term condition with a wide range of symptoms:

- Extreme tiredness (the most common symptom)
- Exercise intolerance
- Insomnia
- Cognitive problems: thinking, memory and concentration
- Muscle or joint pain
- Headaches
- Sore throat
- Flu-like symptoms
- Feeling dizzy or sick
- Fast or irregular heartbeats

The severity of symptoms can vary from day to day, or even within a day.

Long COVID is regularly compared to CFS/ME and some have hypothesised that they may be the same condition. A systematic review found that 25 out of 29 known ME/CFS symptoms were reported by at least one Long COVID study, showing significant overlap between the 2 conditions.

(Wong TL, Weitzer DJ. Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)-A Systemic Review and Comparison of Clinical Presentation and Symptomatology. Medicina (Kaunas). 2021 Apr 26;57(5):418; Wildwing T, Holt N. The neurological symptoms of COVID-19: a systematic overview of systematic reviews, comparison with other neurological conditions and implications for healthcare services. Ther Adv Chronic Dis. 2021 Jan 28;12:2040622320976979); (https://www.nhs.uk/conditions/chronic-fatigue-syndrome-cfs/)

CFS/ME and infection

- **A 2019 review identified the most common apparently causal events: Infections (64%); stressful incidents (34%) and exposure to environmental toxins (20%).**
- Studies show that chronic low level inflammation and activation of cell-mediated immunity with an increase in inflammatory mediators contribute to the clinical symptoms; inflammation of glial cells and neuronal stimulation may induce chronic pain. Immune dysregulation in ME/CFS has been frequently observed involving not only changes in cytokine profiles, but also in immunoglobulin levels, T- and B-cell phenotype and a decrease in natural killer cell cytotoxicity.
- CFS manifests as slightly increased biomarkers of inflammation and pro-inflammatory cytokines such as IL1, IL6 and TNFα. Additionally, impaired natural killer cell function appears evident.
- There is convincing evidence that in at least a subset of patients, ME/CFS has an autoimmune aetiology, with autoantibodies against various antigens including neurotransmitter receptors.

(Chu L, Valencia IJ, Garvert DW, Montoya JG. Onset Patterns and Course of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Front Pediatr. 2019 Feb 5;7:12; Lyons D, et al. Fallout from the COVID-19 pandemic - should we prepare for a tsunami of post viral depression? Ir J Psychol Med. 2020 Dec;37(4):295-300; Bornstein SR, et al. Chronic post-COVID-19 syndrome and chronic fatigue syndrome: Is there a role for extracorporeal apheresis? Mol Psychiatry. 2021 Jun 17:1–4; Bansal AS, et al. Chronic fatigue syndrome, the immune system and viral infection. Brain Behav Immun. 2012 Jan;26(1):24-31; Sotzny F, et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome - Evidence for an autoimmune disease. Autoimmun Rev. 2018 Jun;17(6):601-609)

Postural orthostatic tachycardia syndrome (POTS)

- Chronic activation of the extended autonomic system, which includes the neuroendocrine and neuroimmune systems, is associated with an increased risk of developing Long COVID. Many POTS symptoms are thought to be related to inadequate control of blood flow, causing dizziness when moving to an upright position, as well as brain fog, palpitations, tachycardia and chronic fatigue, among other symptoms.
- POTS can be triggered by a variety of conditions, including viral or bacterial infections and has previously been implicated in persistent post-viral symptomatology; over 40% of POTS cases thought to be associated with viral infection, possibly triggered by induced autoimmunity or molecular mimicry.
- An increasing number of studies are noting a relationship between COVID-19 and POTS. In previously healthy non-hospitalised patients, 85% had residual autonomic symptoms (including POTS), with 60% unable to return to work.
- One hypothesis connecting POTS with COVID-19 builds on its known interaction with the ACE2 protein expressed on neurons. Researchers hypothesize that this can disrupt the normal regulation of blood pressure mediated by ACE2, leading to hypotension and dysautonomia.

(https://www.hopkinsmedicine.org/health/conditions-and-diseases/postural-orthostatic-tachycardia-syndrome-pots; Aquaro GD, et al., Prognostic value of repeating cardiac magnetic resonance in patients with acute myocarditis, J. Am. Coll. Cardiol. 74 (20) (2019) 2439–2448; Goldstein DS. The possible association between COVID-19 and postural tachycardia syndrome. Heart Rhythm. 2020; 20:31141-43; Blitshteyn S, Whitelaw S. Postural orthostatic tachycardia syndrome (POTS) and other autonomic disorders after COVID-19 infection: a case series of 20 patients. Immunol Res. 2021 Apr;69(2):205-211; Chilazi M, et al. COVID and Cardiovascular Disease: What We Know in 2021. Curr Atheroscler Rep. 2021 May 13;23(7):37)

Macrophage activation syndrome (MAS)

- Macrophage activation syndrome (MAS) is an acute and severe inflammatory syndrome, primary or secondary to infection, rheumatic disease, malignancy or drugs. It is frequently confused with sepsis.
- MAS is a potentially life-threatening complication of rheumatic diseases such as systemic juvenile idiopathic arthritis and systemic lupus erythematosus. It is often considered a type of secondary haemophagocytic lymphohistiocytosis and results from over-activation of T lymphocytes and macrophages leading to a "cytokine storm". Characteristic features are persistent fever, lymphadenopathy, hepatosplenomegaly, cytopaenias (anaemia, leucopaenia, thrombocytopaenia), raised C-reactive protein, falling erythrocyte sedimentation rate, hypofibrinogenaemia, transaminitis, hypertriglyceridaemia and extreme hyperferritinaemia often associated with multi-organ impairment. (Sen ES, et al. Macrophage Activation Syndrome. Indian J Pediatr. 2016 Mar;83(3):248-53)

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How many syndromes are enough?

Symptoms and conditions of Long COVID following other viruses.

A novel virus?

- From the start, health authorities and many others have referred to COVID-19 (or SARS-CoV-2) as a ‘novel virus’.
- Even this winter the BBC Science and Health Correspondent was still saying “The new coronavirus…..was a completely new virus that our immune systems had not experienced before” (https://www.bbc.co.uk/news/health)
- But it’s not a novel virus and nor does it have novel post-viral effects.
- What can we learn from the after-effects of other viruses?

Viruses with post-viral effects

- SARS-CoV-1
- MERS
- Chikungunya virus
- Coxsackie B virus,
- Coxiella burnetii (Q fever)
- Cytomegalovirus,
- Dengue virus
- Ebola virus
- Enteroviruses
- Epstein-Barr virus
- H1N1 Bird Flu
- H7N9 Bird Flu
- Hepatitis A and B
- Human herpesvirus-6
- Legionnaires' disease
- Mumps,
- Parvovirus
- Retroviruses,
- Ross River virus
- Rubella,
- Russian flu virus, 1889 and 1892
- Spanish flu virus, 1918
- Varicella zoster virus
- West Nile virus
- Zika virus

Comparison: Lungs

Long COVID	Symptoms/conditions following other viral infections
Breathlessness/cough	SARS-CoV-1; H1N1 flu; Q fever
Impaired diffusing capacity for carbon monoxide	SARS-CoV-1; MERS; H1N1 flu; H7N9 bird flu
Reduced 6 minute walking distance	SARS-CoV-1; MERS
Lung fibrosis	MERS; H7N9 bird flu
Ground-glass opacity	MERS; H7N9 bird flu

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Lung fibrosis	MERS; H7N9 bird flu
Ground-glass opacity	MERS; H7N9 bird flu

Comparison: Cardiovascular

Long COVID	Symptoms/conditions following other viral infections
Thrombosis	SARS-CoV-1
Hypertension	SARS-CoV-1
Ischaemia	SARS-CoV-1
Arrhythmias	SARS-CoV-1
Sudden cardiac death	SARS-CoV-1
Systolic/diastolic dysfunction	SARS-CoV-1

Comparison: Neurological/mental health

Long COVID	Symptoms/conditions following other viral infections
PTSD	SARS-CoV-1; MERS; H1N1 flu
Depression	SARS-CoV-1; MERS; Spanish flu
Anxiety	SARS-CoV-1; MERS; H1N1 flu
Insomnia	SARS-CoV-1; Spanish flu; Epstein-Barr virus, Coxiella burnetii, Ross River virus, Ebola
Memory impairment	SARS-CoV-1; Ebola
Fatigue	SARS-CoV-1; MERS; most flu epidemics; Epstein-Barr virus, parvovirus, West Nile virus, Enteroviruses, Coxiella burnetii, human herpesvirus-6, Ross River virus, Dengue virus, Ebola virus, Legionnaires' disease, mononucleosis, acute viral hepatitis, Chikungunya virus

Comparison: Other

Long COVID	Symptoms/conditions following other viral infections
Musculoskeletal problems and pain	SARS-CoV-1; acute viral hepatitis; Epstein-Barr virus, Coxiella burnetii, Ross River virus, Chikungunya virus, Ebola
Hypothyroidism	SARS-CoV-1
New-onset diabetes, particularly Type 1	SARS-CoV-1; enteroviruses, Coxsackie B virus, retroviruses, rubella, mumps, cytomegalovirus, Epstein-Barr, varicella zoster virus
Suppressed immune system	SARS-CoV-1
T cell hyperactivation	SARS-CoV-1

Lessons from other viruses: Lungs

- CT scanning after 15 years after SARS-CoV-1 showed that **pulmonary lesions had decreased from 9% at 1 year to 3% at 2 years but had risen to 5% after 15 years**, showing reversal between years 2 and 15. (Zhang, P., et al. (2020). Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: a 15-year follow-up from a prospective cohort study. Bone research, 8, 8)
- However another study showed a **gradual reduction in lung lesions at least up to year 7**. (Wu X, et al. Thin-Section Computed Tomography Manifestations During Convalescence and Long-Term Follow-Up of Patients with Severe Acute Respiratory Syndrome (SARS). Med Sci Monit. 2016;22:2793-2799)
- 5 years after ICU discharge following ARDS, patients' 6 minute walk distance was only 76% of predicted distance and physical functioning had not returned to normal, despite pulmonary function being close to normal. Many other physical and psychological problems were reported. (Herridge MS, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011 Apr 7;364(14):1293-304)
- At 2 years, diffusing capacity for carbon monoxide (DLCO), exercise capacity and health status remained impaired in a significant number of patients. The 6-minute walk distance increased significantly up to 6 months and remained steady thereafter but was still low compared to the general population. (Ngai JC, et al. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. Respirology. 2010;15(3):543-550)

Lessons from other viruses: cardiovascular disease (CVD) events

- **35% of pneumonia hospitalisation cases had CVD events; risk was highest during the first year and remained significantly higher than among controls up to 10 years**. (Corrales-Medina VF, et al. Association between hospitalization for pneumonia and subsequent risk of cardiovascular disease. JAMA. 2015;313(3):264-274. doi:10.1001/jama.2014.18229)

Other viruses: Musculo-skeletal

- A study with hip joint MRI showed that the volume of **femoral head necrosis decreased from 39% at baseline, 30% at year 2, to 26% at year 15**. (Zhang, P., et al. (2020). Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: a 15-year follow-up from a prospective cohort study. Bone research, 8, 8)

Lessons from other viruses: Mental health

- 3-4 years after recovery from SARS-CoV-1, **42.5% had experienced at least 1 active psychiatric illness**. (Lam MH, et al. Mental Morbidities and Chronic Fatigue in Severe Acute Respiratory Syndrome Survivors: Long-term Follow-up. Arch Intern Med. 2009;169(22):2142–2147)
- **A systematic review of the mental health of people with SARS found that PTSD stress symptoms were present in high proportions of survivors even as late as 4-5 years after the initial infection.** (Gardner, P.J. et al (2015) Psychological impact on SARS survivors: Critical review of the English language literature Canadian Psychology 56(1), p.123-5)
- **Survivors of Spanish flu (1918) suffered mental health consequences**: depression, sleep disturbances, mental distraction, dizziness and difficulties coping at work. Brain inflammation or encephalitis sometimes emerged as long term effects, known as **encephalitis lethargica** (EL) at the time. UK physicians and researchers were also reporting increases in neuropathy, neurasthenia, meningitis, degenerative changes in nerve cells and a decline in visual acuity. Other doctors of that time reported patients exhibiting a high degree of general hyperkinesis, a difficulty in maintaining quiet attitudes, abruptness and clumsiness, and "explosive motor release of all voluntarily inhibited activities". (https://www.medscape.com/viewarticle/951053?uac=116656PT&faf=1&sso=true&implD=3372648&src=mkm_covid_update_210513_MSCPEDIT)

Lessons from other viruses: Fatigue

- 3-4 years after recovery from SARS-CoV-1, **40% reported persistent fatigue and 27% met the CDC criteria for chronic fatigue syndrome**. (Lam MH, et al. Mental Morbidities and Chronic Fatigue in Severe Acute Respiratory Syndrome Survivors: Long-term Follow-up. Arch Intern Med. 2009;169(22):2142–2147)
- SARS survivors suffered significantly reduced exercise capacity 2 years after infection (Ngai JC, et al. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. Respirology. 2010 Apr;15(3):543-50).
- **5 years after Q fever infection, 69% of patients reported fatigue. CDC criteria for chronic fatigue syndrome were fulfilled by 42% of cases.** (Ayres JG, et al. Post-infection fatigue syndrome following Q fever. QJM 1998;91: 105-23)

Lessons from Ebola

- **2-3 years after Ebola infection, some survivors were still experiencing eye pain, blurred vision, hearing loss, difficulty swallowing, difficulty sleeping, arthralgias, memory loss and confusion**. (Clark DV, et al. Longterm sequelae after Ebola virus disease in Bundibugyo, Uganda: a retrospective cohort study. Lancet Infect Dis. 2015 Aug;15(8):905-12)
- At 12 months follow-up after Ebola infection, the prevalence of symptoms was urinary frequency 15%, headache 48%, fatigue 18.%, muscle pain 3%, memory loss 29%, joint pain 47.5% and uveitis (eye inflammation) 33%. On examination, abnormal abdominal, chest, neurologic and musculoskeletal findings were also seen. Other than uveitis, the prevalence of these conditions declined with time. (PREVAIL III Study Group, A Longitudinal Study of Ebola Sequelae in Liberia. N Engl J Med. 2019 Mar 7;380(10):924-934)

Lessons from other viruses: Medication

- 12 years after SARS infection, some of those given **high-dose pulses of methylprednisolone had long-term systemic damage** associated with serum metabolic alterations. (Wu Q, et al. Altered Lipid Metabolism in Recovered SARS Patients Twelve Years after Infection. Sci Rep. 2017;7(1):9110)