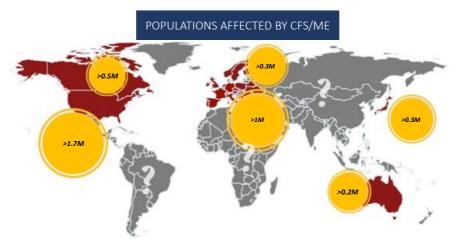


Post Covid-19 Pandemic & Chronic Fatigue Syndrome / Myalgic Encephalomyelitis (CFS/ME) potential spike.

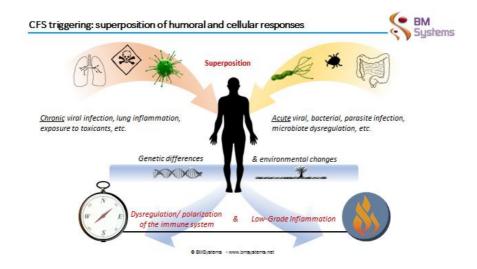
Why does it appear likely that the current coronavirus pandemic caused by the ssRNA SARS-CoV-2 virus could trigger a worldwide spike in CFS/ME in the coming 6-18 months?

 CFS/ME is not a rare disease. <u>CDC estimates</u> that between 836 000 to 2.5 million Americans suffer from the disease. <u>Euromene</u> (EU CFS/ME program) estimates between 730 000 to 4.1 million. ME/CFS costs the U.S. economy about \$17 to \$24 billion annually in medical bills and lost incomes.



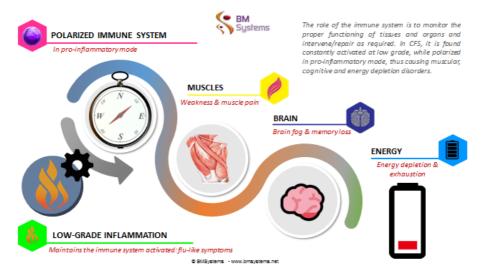
Lowest estimates of CFS/ME patients number worldwide, based on available data.

• CFS/ME PATHOLOGY: The disease is triggered by overlapping immune responses that misguide the actions of the immune system. These are often caused by acute viral infections, similar to those provoked by SARS-CoV-2.

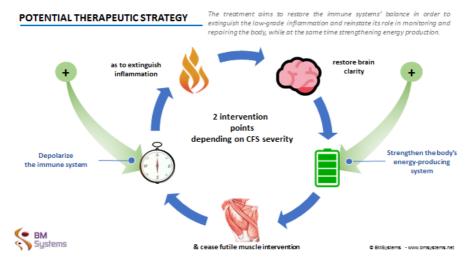


 LOW-GRADE INFLAMMATION: The immune system monitors the functioning of tissues and organs and intervenes/repairs as required. In CFS, it is found constantly activated at low grade and in pro-inflammatory mode, causing muscular, cognitive and energy depletion disorders.





- NO THERAPY: Due to limited understanding of the pathology, no therapeutics exist to address this complex and debilitating disease.
- BMSYSEMS' THERAPEUTIC DISCOVERY (CADI-T1031): BMSystems has discovered and offers
 the world's first therapeutic solution for CFS/ME. Our treatment restores the balance of
 the immune system, extinguishing the low-grade inflammation and reinstating its role in
 monitoring and repairing the body, while at the same time restoring the organism's energy
 production machinery.



- Our proprietary therapeutic protocol has successfully completed the proof-of-concept stage and will enter Phase II clinical trials with our confidential development partner. The therapy could help manage the anticipated spike of CFS patients due to Covid-19 epidemic.
- For all detail see above and for more information: https://www.bmsystems.org/projects
- For more information about <u>CFS/ME French Association</u>



FULL TEXT

CFS/ME is a complex and debilitating disease that imposes a burden of illness on millions of people around the world. CFS/ME is a serious, chronic and complex systemic disorder characterized by a state of deep exhaustion that is not due to intense physical or intellectual activity and is not relieved by rest. The pathology involves central nervous system and immune system disorders, characterized by extreme fatigue that severely limits the ability to perform ordinary daily activities. CFS/ME onset may occur suddenly, such as following a viral infection, or gradually.

The frequency of CFS is variously appreciated, depending on the criteria of definition, with prevalence between 0.11 - 0.56%, in Western countries. The ratio of women to men is around 3/1, with predominance in young adults (20-45 years) but with a possible attack at any age and a possible genetic predisposition. CDC estimates that tetween 836 000 to 2.5 million Americans suffer from CFS, with often severe degrees of disability generating high health costs and distress. Euromene (EU CFS/ME program) estimates between 730 000 to 4.1 million.

CFS/ME pathophysiology has a multifactorial origin involving infectious (viral infections) and maintenance (psychological) factors as well as the persistence of inflammatory (low-grade inflammation), immunologic (as abnormal cytokine production) and muscular (mitochondrial dysfunction and failure of bioenergetic performance) abnormalities at the origin of multiple dysfunctions (endocrine, neuromuscular, cardiovascular, digestive and others). Symptoms include severe fatigue or exhaustion, unrefreshing sleep, weakness, muscle and joint pain, impaired memory or mental concentration, tender lymph nodes, sore throat, headaches, and sleep dysfunction.

Patients with CFS are mainly affected by an immune condition that may be seen as an amphipolarization of their immune system, i.e. a condition where their immune system tries to simultaneously resolve infection-like hazards that require opposing strategies (known as humoral and cellular responses). These may be triggered when acute single strand RNA (ssRNA) viral infections, such as the ones caused by influenza or SARS-CoV-2 viruses, are superimposed on a low-grade inflammatory background, such as the one caused by chronic double-strand DNA (dsDNA) infections as HPV, EBV, CMV, toxoplasma or even chronic exposure to toxic agents.

Although data on CFS/ME remains limited because the pathology is often misdiagnosed and, in the past, has had limited success in raising awareness, the first association between viral pandemics and CFS/ME-like symptoms was provided by investigators at the Johns Hopkins Hospital through a retrospective analysis of military cohorts during the 1957-1958 Asian influenza pandemic [1]. More recently, a Norwegian national study showed that the percentage of CFS/ME occurrence doubled following the 2009 influenza A (H1N1) pandemic [2].

More alarming data are provided by the previous 2003 SARS and 2015 MERS epidemics, relating the virus outbreaks to increased CFS/ME onset. Of 233 Hong Kong hospital SARS survivors assessed 4 years after the viral outbreak, over 40% had active psychiatric illnesses, 40.3% reported a chronic fatigue problem, and 27.1% were diagnosed with CFS/ME [3]. Similar data was retrieved from 229 Toronto SARS survivors, where 10% presented CFS/ME symptoms, 3 years following infection [4]. For comparison, less than 1% of people worldwide meet chronic fatigue syndrome criteria.



An equivalent relationship among chronic fatigue, depressive symptoms, and post-traumatic stress symptoms (PTSSs)- i.e. among the most prominent CFS/ME symptoms- is found among 2015 Middle East respiratory syndrome (MERS) survivors in South Korea. Of 148 survivors assessed at 12 and 18 months after the MERS outbreak, 72 (48.65%) presented chronic fatigue, depressive symptoms, and PTSSs [5].

It appears therefore likely that the current coronavirus epidemic, caused by the ssRNA SARS-CoV-2 virus could trigger a worldwide spike in CFS/ME in the coming 6-18 months.

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- 3 Lam, M. H. *et al.* Mental morbidities and chronic fatigue in severe acute respiratory syndrome survivors: long-term follow-up. *Arch Intern Med* **169**, 2142-2147, doi:10.1001/archinternmed.2009.384 (2009).
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