Wildfire's Infectious Diseases Blog – 'The Pathogenda'

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OK, this week I thought it would be nice to segue away from the saddening events playing out in the Ukrainian crisis and compare and contrast some sequelae that are already making themselves felt globally. Like politics, medicine can change trajectories swiftly as positive interpretation of events are tempered by stark, cold realities, such as rising case fatalities from disease, war, displacement and the remembrance of missed opportunities to intervene. A case in point is the role of anti-inflammatories in severe, hospitalised infectious disease, especially in viral URT disease such as COVID. Where did dexamethasone and the like suddenly appear from and why didn't the much vaunted directly acting agents (antivirals) change the course of the pandemic? Who wears the crown now?

Once the bane of the GP with a significant aged patient population, crumbling, constantly in pain, requiring of frequent calls, home-help and disfigured and depressed by the condition, the treatment of rheumatoid arthritis and other inflammatory joint diseases and the lives of those blighted by this condition has been transformed by the use of biologic medicines. These targeted therapies are usually added to the treatment regimen when background conventional disease-modifying antirheumatic drugs (DMARDs) are insufficient. With the newer drugs, remission is now an achievable goal, especially for patients with newly diagnosed rheumatoid arthritis. What is even more cheering is that the wide availability of biosimilars for tumour necrosis factor α (TNF-α)–blocking agents has contributed to lower drug prices and improved access for patients generally. So, as COVID came to be seen more as a immunological disease manifesting itself in progressive cases through dysregulated inflammatory pathways following a viral 'trigger', the door then opened to NSAID and steroid use as well as the revolutionary new biologicals to reduce hospitalisation rates, ventilator use or even fatalities within severe, hospitalised patient cohorts. Some of this optimism has proven well founded, but with caveats around optimal dosages, other leads have withered on but still will not fall from the vine.

To put this into some sort of perspective, to date, very few of the much-hyped 'early win' COVID-19 treatments have been shown to be effective in significantly improving outcomes, period. Subsequent to extensive, including meta, analyses, the Remdesivirs, convalescent plasmas, Calquence and Kevzaras of this world failed to show statistical evidence of efficacy in hospitalised patient trials and were rightly abandoned. However, the stalwarts of RA, systemic glucocorticoids consistently demonstrated improvements in survival when administered to moderately or severely ill patients and are now recommended in both the WHO guidance for the clinical management of COVID-19 and the National Institutes of Health COVID-19 treatment guidelines. Although the WHO guidance does not recommend any particular glucocorticoid dose, the National Institutes of Health guidelines recommend 6 mg of dexamethasone once daily for 10 days or until hospital discharge for hospitalised adults requiring supplemental oxygen or mechanical ventilation. The target of GCs is known to be mRNA mediated expression of proinflammatory proteins, but details are still evasive regarding anti-COVID activity in any detail. 'They work' is the general message here.

Going forward, how should we interpret the recent study by the COVID STEROID 2 Trial Group? (an international, multicentre randomised clinical trial comparing 2 alternative doses of glucocorticoids in critically ill patients with COVID-19).The results are supportive of improved outcomes with 12 mg/d of dexamethasone, but not definitive, and do not satisfy the usual criteria to support change in practice. However, clinicians will still wonder if there is a risk of a type II error (a false negative – they are all optimists), with insufficient power to confirm a real difference of major importance to clinical practice and public health. In this regard, the consequences of a type II error are of greater importance than a type I error (a false positive – optimism breeds over-enthusiasm for pet therapies. See Ivermectin and hydroxyquinoline), particularly in resource-limited settings with widespread availability of glucocorticoids and limited access to other immune modulators. Additional trials, which are underway are needed to clarify this important clinical question, with the results ideally combined in a prospective meta-analysis.

https://jamanetwork.com/journals/jama/fullarticle/2785531

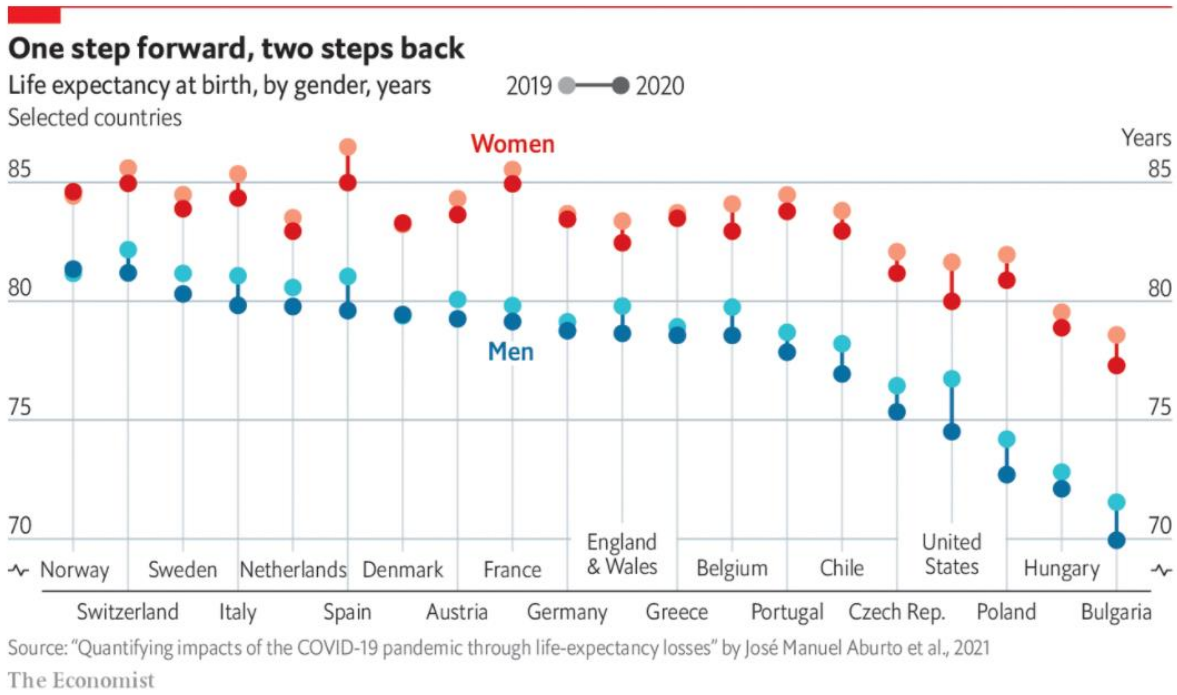
And if you still don't believe me, here is some nice evidence that uncontrolled inflammation really is BAD for you. Something I noted working in HIV in the Noughties, myocardial events were higher in untreated cohorts. Quel surprise? Many were not convinced at the time but I remembered both my lessons in Hepatitis B relating to hepatocellular carcinoma, and *Mycobacterium tuberculosis* and fibrosis and cancer – any bells ringing? The Relationship between Tuberculosis and Lung Cancer (nih.gov); https://www.nature.com/articles/d41586-022-00468-x

This welter of inflammatory disease has actually reduced average lifespans globally. HIV didn't manage that, H1N1/2009pdm filed to give a measurable blip. It took an obscure common cold virus to reverse many decades of disease control, public healthcare and improved standards of living. In a study of 29 high income countries, the U.S. experienced the largest decline in life expectancy in 2020 and, unlike much of Europe, did not bounce back in 2021. It was also the only country whose lowered life span was driven mainly by deaths among people under 60. Dying from COVID robbed each American of about a decade of life on average. As a whole, US life expectancy fell 2 years—the largest such decline in almost a century. Neither World War II nor any of the flu pandemics that followed it dented American longevity so badly. The lesson here? Keep healthy, keep a normal BMI for your height, believe the hype around vaccines and honestly, pay for healthcare that is fee at the point of access:

https://www.medrxiv.org/content/medrxiv/early/2022/02/24/2022.02.23.22271380.full.pdf

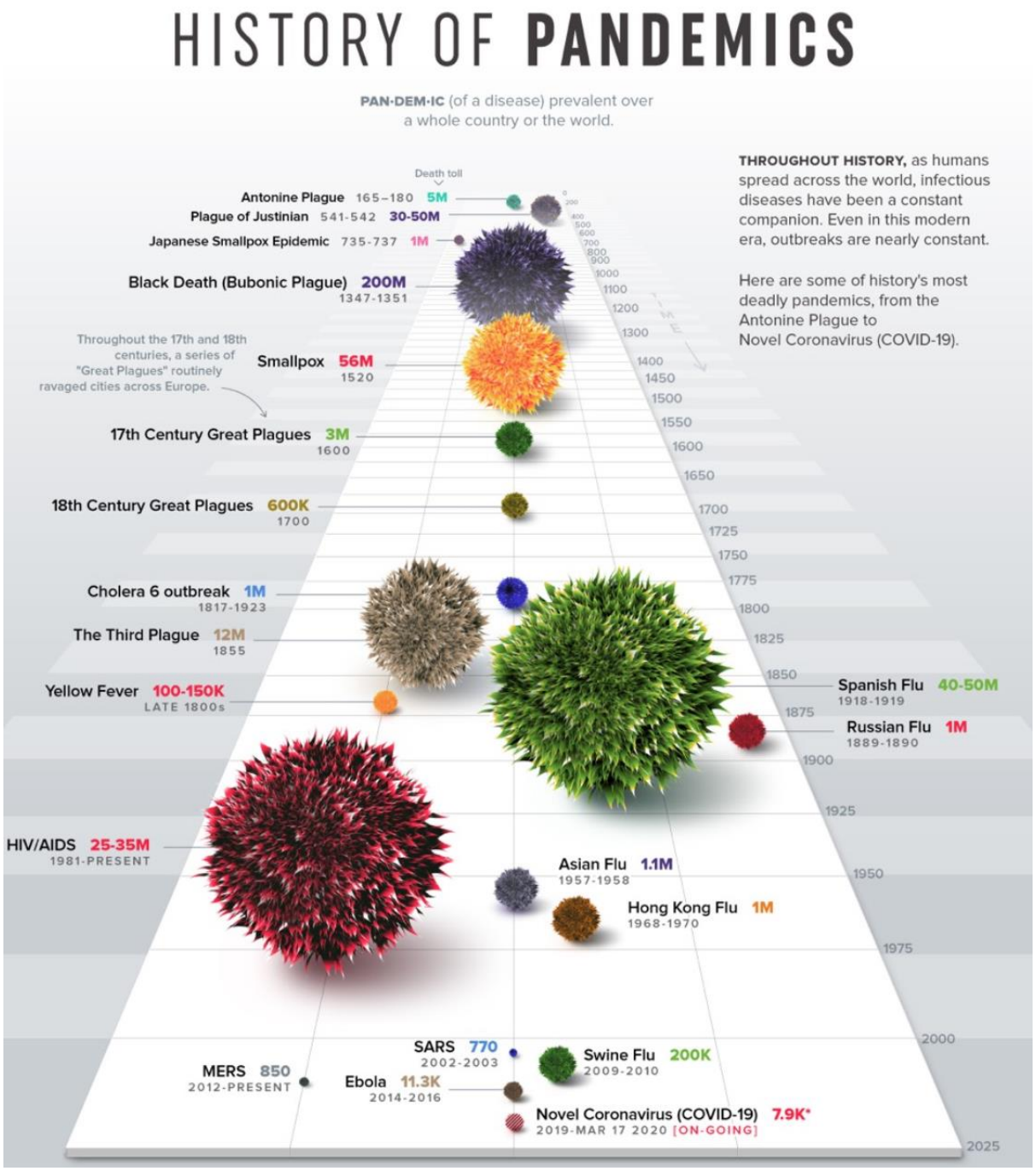
During 'The Big Cough' as we may come to regard the COVID pandemic, the Nordic countries seem have fared better than many, but then their per capita spend on healthcare tops the league.

Last year only Danes, Norwegians and Finnish women enjoyed slight gains in longevity



So, as per the opening lines regarding medicine, like politics, rapidly changing direction as evidence mounts. We should be open to change based upon emerging facts. We still have a lot to learn from host pathways; knowledge of these complex interactions with outside factors e.g. viral disease, sets us free to think outside the box and in such freedom lie solutions.

What is sad is that although the UK's expenditure has risen by 11% during the course of the pandemic, we are still 'middle of the road' when it comes to percentages (10%) comparted to the US's 17%. Hidden in there, of course, are hugely confounding factors such as 65% of US spend being 'voluntary contributions' (read: private healthcare) vs central funding and diverse regional inefficiencies or inequalities. It is data as given above that will help us count the true cost of the pandemic and perhaps better target spend next time around. Sadly there will be a 'next time around' as high CFR pandemics are like wars and revolutions – they come around about once per hundred years ('ish) and radically change life as we know it. There, full circle for us also.



**Today's total deaths for COVID = 6M. About the size of the Antonine plague.*

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