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EDITORIAL

Coronavirus disease 2019 as a syndemic

> On hearing ill rumour that Londoners may soon be urged into their lodgings by her Majesty's men, I looked upon the street to see a gaggle of striplings making fair merry, and no doubt spreading the plague well about. Not a care had these rogues for the health of their elders!
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> Samuel Pepys, Diaries, London 1664.

It seems that human nature has not changed much over the past third of a millennium. Contemporary newspapers are replete with photographs of people ignoring advice about social distancing. Many, but not all, of these are young; consistent with the perception by adolescents of their own immortality, coupled with a desire for immediate gratification, even at the risk of future consequences. As anticipated by Pepys, these consequences are often not visited upon the generation that took the initial risks.

The plague currently affecting us is coronavirus disease 2019 (Covid-19), found more frequently than expected in senior citizens, males and in people of non-Caucasian background. The causative agent, SARS-CoV-2 is a generally mild virus acquired by the respiratory route that spreads systemically. It tends to wreak havoc in the lungs, kidneys, heart and clotting systems of people who are old and/or have comorbidities, particularly diabetes, obesity and hypertension.[1-3] A failure of the immune system to control initial infection is compounded by the tendency of the senescent immune system to switch into inflammatory overdrive.[4] Several articles in this journal have documented this and considered some potential contributory factors worthy of further exploration.[5,6]

As reviewed by Teymoori-Rad and colleagues, deficiency of vitamin D is common and may have genetic predispositions.[5] The active form of this multifunctional hormone increases the level of IkBalpha that restrains inflammation triggered by NFkB signalling which, in in vitro experiments, is achieved without increasing the quantity of respiratory syncytial virus infection.[7] Vitamin D deficiency is associated with an excess of respiratory viral infections and a randomised controlled trial (RCT) supports clinical benefit from dietary supplementation.[8,9] Full anabolism to the active form of vitamin D is effected by sunlight, so people with darker skin colour may have increased risks of deficiency.[5]

Immune senescence has multiple components, including atrophy of the thymus in early adulthood and the progressive acquisition of immunocommitted T-cells as individuals experience multiple virus infections as they age.[6,10] Remarkably, most of these differentiated T-cells are specific for cytomegalovirus (CMV) and their abundance can be reduced by valganciclovir.[10,11] This virus is acquired preferentially by people from non-Caucasian backgrounds and its prevalence increases with age.[12,13] A study comparing monozygotic twins with dizygotic reported that most of the variance in immune parameters was non-hereditary and driven by CMV.[14] A recent publication shows that the prevalence of CMV IgG antibodies is higher among those with Covid-19 severe enough to require hospitalisation.[15] There is a known association between CMV and mortality in the general public and in stem cell transplant patients.[16-18] An RCT in the latter reports significantly reduced mortality from the CMV-specific antiviral drug letermovir.[19,20]

Rather than considering these vitamin D and CMV candidates as competitors with SARS-CoV-2 for causality of mortality, we should be considering that they and other factors could be interacting in a complex web of Venn diagrams to deliver this end. Covid-19 should thus be thought of as a multifactorial syndemic caused by contributions from multiple overlapping epidemics.[21] As well as the biological factors mentioned above, candidates include the social epidemics of diabetes, obesity (sometimes combined into the term diabesity), social deprivation and racial prejudice that conspire to leave many at risk of disease living in crowded conditions and working in people-facing occupations. Add in inadequate financial provision to take time off work when they become exposed to individuals with SARS-CoV-2 and it becomes clear how many interactions may conspire to sustain the pandemic. Potentially, action taken against any single component of a syndemic could reduce the severity of disease and could deliver results rapidly because licensed treatments exist for them already. The interactions within a syndemic are so complex that placebo-controlled RCTs are essential. Several RCTs are underway to determine if supplementation with vitamin D can reduce the severity of Covid-19 but, despite the body of evidence summarised above, I could not find any RCTs evaluating anti-CMV therapy in the setting of Covid-19 on Clintrials.org.[5]

Fortunately, help is on its way with four vaccines that have provided remarkable protection in Phase 3 RCTs against the initiating SARS-CoV-2 (BioNTech/Pfizer; Gamaleya Center/Russian Direct Investment Fund; Moderna; Oxford University/AstraZeneca)

with one licensed already (BioNTech/Pfizer). It is understandable, but frustrating, that information about this important topic becomes available through company press releases based upon planned interim analyses of the primary endpoint from ongoing clinical trials. This is an important parameter, and what the trial data safety monitoring board will be following closely, but much more is required. We need to see the protocol describing the inclusion and exclusion criteria, and descriptions of the ages and demographics of those recruited. We want to see the details of the intention to treat (ITT) population (defined as all those who signed a consent form), the modified ITT (usually defined as all those randomised people who received at least one dose of vaccine/placebo) and the per protocol population (typically those who completed the protocol as planned, often censored to make them become eligible at a fixed time after the final dose of vaccine). Providing just one overall number for efficacy is potentially misleading. Likewise, describing the number of volunteers who were recruited into the trial rather than the smaller numbers used to calculate each of the populations defined above can give a false impression of the confidence surrounding the headline figure of efficacy. Nevertheless, we have four vaccines that have reported interim results well above the threshold set by regulators to indicate success. These remarkable results are all the more impressive when the two vaccine platforms (RNA; recombinant adenovirus) have never before led to a licensed vaccine. The Oxford University/AstraZeneca recombinant chimpanzee adenovirus construct had apparently higher potency in a group given a lower dose followed by a full dose, presumably because the lower dose induced less of an immune response against the vector rather than the insert of SARS-CoV-2 spike protein.[22] Further dose ranging studies are planned, including collaboration using the Gamaleya construct which immunises with human adenovirus 26 followed by human adenovirus 5, each containing the spike protein. Further such prime-boost schedules can be explored once more than one vaccine is licensed. Meanwhile, the challenge now is to acknowledge practical problems like −80°C storage temperatures required for the RNA vaccines and turn manufactured vaccine doses into vaccination doses delivered to the elderly and to health care workers.

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