Lack of validity in concepts driving development of SARS-CoV2 vaccines

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Abstract: We have discussed earlier that current approaches to vaccination assume without proof that:

a. following immunization most individuals are at similar risk of disease.

b. relevant host resistant mechanisms (innate and/or acquired immunity) have been identified, and can be targeted appropriately to boost resistance

c. after vaccination, individuals within a population react immunologically in the same way in terms of protective antibodies and/or cell-mediated reactivity (one size fits all) with equivalent and minimal side effects; and

d. vaccination dose and frequency of administration is invariant in the population.

These assumptions have been applied to widespread delivery of vaccines for a number of infectious diseases, with effective control for many of those. However, a clear weakness of this approach is that it discounts the growing evidence for individual variability in risk, in immune responsiveness, and in response to different doses of vaccine, and by routes of delivery (induction of systemic immunity *versus* local intra-nasal mucosal immunity). These issues came to the fore while tailoring individual approaches to cancer therapy, but are now becoming more concerning as we come to grips with novel emerging infections, as has been highlighted during the recent SARS-COV-2 pandemic.

We discuss below in more detail how innate immunity is likely an important component of viral resistance, and that viral responses to the innate immune system can help explain mutagenesis of SARS-CoV2 virus in the host. We also suggest that the inattention to mucosal immunity as a major component of respiratory virus infection, with instead a focus on induction of systemic immunity for SARS-CoV2 through conventional intramuscular injection, is a major error, and may have led to a gross misrepresentation of current vaccine efficacy and utility.

Finally, we recapitulate our previous discussions of a characteristic epidemiology of this infection as it developed in distinct areas throughout the globe over the past 3 years, which led us to conclude that this reflected globally dispersed fragmented viral laden dust clouds brought down haphazardly to ground by local meteorological conditions and defined by capricious scales of turbulence. The emergence of new infection clusters of varying sizes independent of popular movement is readily explained on this basis. This hypothesis is testable, and offers hope that 'lead-time" for future pandemics may be gained by sampling microbial content in the high stratosphere.

1.Origin and epidemiology of SARS-CoV-2 (and other emergent) infections.

For the past 30 months, the world has been ravaged by a pandemic caused by a coronavirus infection recognized initially in late 2019 in Wuhan, China. By mid-2020 there had arisen global consensus that the way forward from the socioeconomic and medical morass which had occurred was through rapid development and implementation of a universal vaccination program. However, unlike past precedents, this has taken place in the absence of consensus on the origin and epidemiology of infection; without detailed knowledge and investigation into the nature of natural host resistance to the pathogen; and by "speed-tracking" novel vaccine designs to clinical use, again in the absence of refined knowledge of possible short-term and longer-term implications of this vaccine's administration

We have suggested in many publications (see 1-4) that there is a compelling argument to be made that the origin of the current SARS-CoV-2 outbreak, and possibly of other emergent novel infections, is attributable to an "in-fall" of infectious particles from the stratosphere (5). We can highlight many of the arguments supporting this notion with specific attention to a series of so-called COVID-19 mystery community transmissions which occurred in a defined arc across the inner Western and outer Northern suburbs of Melbourne, Victoria in May – June 2020 (6) and in May-June 2021 (7). These could not be traced to any direct infected contacts nor could they be directly genomically linked to any known infection clusters (e.g. among infected international travellers in hotel quarantine or in aged care and nursing homes). As a consequence of the government response to this perceived emergency, large numbers of PCR COVID-19 tests on oro-nasal swabs were conducted (> 30, 000 per day at peak) with all positive cases quarantined at home. Contact tracing was conducted by teams of experienced tracers, yet despite a total clamp on individual mobility, new mystery outbreaks continued to occur in the 2020 and 2021 epidemics in Victoria. Detailed analysis in 2020 showed that more than 25-30% of all tracked Covid-19 variants were genomically-unlinked "mystery infections" without a known infection contact (6) as shown in Figures 1 and 2. In the smaller 2021 epidemics many of the viral variants of concern (PANGO classification) were clearly mature human-passaged virions, many of which were also identified in the large Indian April-May2021 epidemic. The public domain data in Victoria support the hypothesis that a heterogeneous set of these 2021 "Indian" variants delivered into a tropospheric aerosol plumes (7), were transported by prevailing tropospheric global wind systems via the Indian Ocean and host responses to infections, and in turn contrasts that evidence with the approach used in vaccination against SARS-CoV-2. Southern Ocean (Roaring Forties West to East on the 40º S Latitude line) to Victoria, Australia. Indeed, as we have and others have argued before, there is precedent for such global wind transportations in the history of past Influenza virus pandemics in the last 100 years and the present observations relating to COVID-19 events in Australia are likely but one of many such incidents (8, 9). These confirmed unlinked "mystery case" infections in Victoria, Australia in 2020 and 2021 are interpretated as a clear signature of viral in-fall from the troposphere leading to a virus contaminated environment. This leads to the ignition of respiratory tract COVID-19 infections in unsuspecting victims who introduce the infection by touching their nose and mouth with their contaminated fingers. As we have established from public domain data, the major viral amplifications occur in immune defenceless elderly subjects with co-morbidities who spread the viral particles via aerosols to contaminate their own closed environment, with trillions of virions facilitating further spread across multiple aged care facilities (6).

The discussion that follows provide a summary consensus view of the current knowledge regarding mammalian host responses to infections, and in turn contrasts that evidence with the approach used in vaccination against SARS-CoV-2.

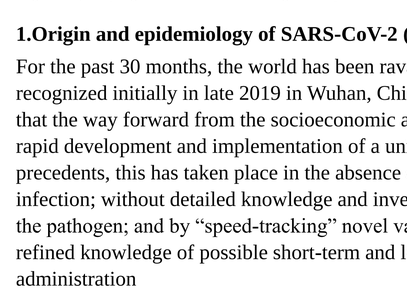

Figure 1: Lindley & Steele. *Scand J Immunol. 2021 (ref 6)*

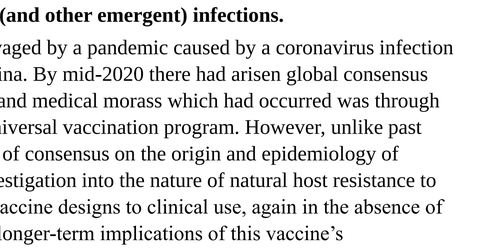

Figure 2 Transmission over time of all SARS-CoV-2 cases in Victoria 2020. Lindley & Steele. *Scand J Immunol. 2021 (ref 6)*

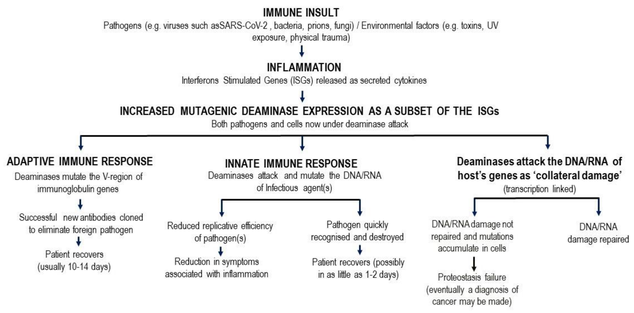

Figure 3: Model linking downstream innate and adaptive immune changes followjng pathogen insult.

2. Innate immunity to pathogens: Mammalian immunity in general, including for SARS-CoV-2, has both an innate and adaptive arm. Innate immunity acts rapidly to control viral replication in infected healthy subjects through type I and type III interferon inducible anti-viral immunity, primarily deaminases which attack DNA or RNA of invading viruses by extensively mutating their genomes with C-to-U (T) and A-to-I(G) mutations, crippling its replicative efficiency (10,11). Elderly patients lacking this rapid innate response are at very high risk for severe outcomes following SARS-CoV-2 infection, including increased morbidity and mortality (12). Type1 and III interferon inducible genes include APOBEC and ADAR, which as described in Figure 1 and elsewhere (5,6) can also play a role in "haplotype switching" of SARS-CoV-2-expressed genes, leading in turn to the diversification of the virus genetic pattern seen in some subjects, but not in those with impaired innate immunity. Figure 3 shows the causal links between deaminase mutagenic activity, SARs-Cov-2 infection, and the role of the host innate and adaptive immune response, and the subsequent possible accumulation of collateral cell damage (see also (13)).

Innate immunity can be "trained" to provide improved immunity on reinfection with the same, and possible even other, pathogens (14), helping explain why infant mortality, and even adult mortality, is less in Bacillus Calmette-Guerin (BCG) vaccinated cohorts (BCG admixed with adjuvants is an excellent inducer of innate immune responses) than in non-vaccinated cohorts from the same population (15). Even live-attenuated vaccines for tuberculosis, measles, and polio can "train" the innate immune system, likely involving histone modifications and epigenetic reprogramming of monocytes to develop an inflammatory phenotype, and improved broad resistance to other infectious diseases, of which SARSCoV-2 infection may be an example (15,16). Comparisons of innate immune responses to Influenza and SARS-CoV-2 in nasal washes from infected adults suggested there was some difference in innate responses following SARS-CoV-2 infection, with decreased IFN-associated transcripts compared with influenza-infected individuals (17). Importantly, comparison of subjects post natural infection vs SARS-CoV-2 vaccination (SARS-CoV-2 BNT162b2 mRNA) showed that only in naturally infected patients, and not vaccinated individuals, was exposure associated with heightened clinically significant mucosal immunity (see below and (18)).

33. Adaptive (acquired) T and B lymphocyte mediated immunity: Unlike the innate immune response, acquired immunity takes some 10–14 days post pathogen exposure to become active, but in general shows much greater diversity for pathogen recognition and is primarily responsible for immunologic memory. Deliberate controlled priming by vaccination exposure to pathogen moieties had been claimed to generate great successes in global infectious disease control (but see 19,20 for a critical appraisal). Not surprisingly then considerable effort was directed to this aim for SARS-CoV-2, focusing on immunity to the receptor-binding domain (RBD) of the spike (S) protein of SARS-CoV-2 which controls viral entry into cells. It has become very apparent that there is considerable heterogeneity in epitope recognition within different individuals/populations, and this has likely contributed to variable efficacy in vaccine utility (13). However, what has remained unexplored is the relative importance of mucosal vs systemic immunity in natural or vaccine-induced protection, with most studies focusing on the (more easily measured/quantitated) systemic IgG response! We have discussed this issue in depth elsewhere (13) and highlight more issues in the following.

4. Mucosal immunity and resistance to/recovery from SARS-CoV-2: It has been known for many years, that the best form of protective immunity for pathogens invading by the nasal or oral route are local secretory IgA responses (21). Recent analyses on SARS-CoV-2 reinfections and transmissions in vaccinated individuals, and studies assessing immunization against influenza and SARS-CoV-2 are consistent with this concept (22,23).

Measurement of humoral responses to SARS-CoV-2 and analysis of specific neutralizing antibodies in the serum, saliva, and bronchoalveolar fluid of 159 patients following natural infection with SARS-CoV-showed that early viral specific humoral responses were dominated by IgA antibodies with peaks during the third week post-infection, with IgA contributing to virus neutralization to a greater extent than IgG or IgM antibodies (24). Anti-viral IgA serum concentrations decreased after 1 month but neutralizing IgA remained detectable in saliva for up to 10 weeks. An independent study also concluded that while serum neutralization and effector functions correlated with systemic SARS-CoV-2-specific IgG responses, mucosal neutralization was associated with nasal SARS-CoV-2- IgA, along with less severe disease (25). Animal (mice) studies have shown that unlike a systemic (im) vaccination protocol, only an intranasal dose of adenovirus vaccine induced high levels of neutralizing antibodies, enhanced both systemic and mucosal IgA and T cell responses, and prevented SARS-CoV-2 infection in both the upper and lower respiratory tracts (26). The validity of mucosal immunization for protection was confirmed in an independent vaccine study in macaques (27). Multiple other studies have reached similar conclusions regarding the importance of induction of mucosal immunity for protection against pathogens targeting the respiratory system (28-30), results consistent with evidence for an increased susceptibility to SARS-CoV-2 in IgA deficient subjects (31).

5. Risk of SARS-CoV-2 vaccines

In the early period following introduction of novel SARS-CoV-2 vaccines, it gradually became apparent that there was a significant unanticipated adverse effect (venous thromboembolism, VITT) described in a subpopulation of subjects (32), leading eventually to reluctance in many countries to continue use of this particular vaccine. Other groups have focused on the theoretical risk associated with other novel vaccines (especially mRNA vaccines), arguing that their "rush into service" has ignored potential concerns with their use, particularly the concern regarding induction of autoimmune reactivity (33-35). Indeed a comparison of immunogenic epitopes in SARS-CoV-2-S proteins, and other SARS-CoV-2 proteins with human protein concluded that only one immunogenic epitope in SARS-CoV-2 had no homology to human proteins, and that many of the overlaps with human proteins could theoretically help explain some of the symptoms associated with the pathogenesis of SARS-CoV-2 (36).

6. Conclusions: There is evidence that we are now approaching an entrenchment phase in the response to the SARS-CoV-2 pandemic, with evolution of less virulent viral variants, better protection of vulnerable population cohorts (especially the elderly), and adherence to better public health measures all combining to improve the overall outlook. At all levels, politically, sociologically, ethically, scientifically and medically, there have been instances of major mismanagement and misunderstanding, coupled with gross errors of judgement, which have clearly cost lives. As discussed above there is still concern that we have failed to recognize the importance of implementation of basic science knowledge, both new research and understanding old observations, which even now would likely improve the future course of the disease. It is clear too that we need to remain vigilant, having implemented so many previously untried and untested therapies, for the appearance of new signs and symptoms in treated patients which are early indications of adverse events. As stressed before, we would argue also that critical evaluation of evidence for a "viral infall" from the stratosphere as a source of this (and previous/future epidemics) may highlight ways we can begin to develop "early warning systems" (37).

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