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Long-Term Organ Complications: The True Public Health Concern in SARSCoV-2 Infection

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Abstract

The collective considerations presented here lead to a crucial question: What truly constitutes the primary public health challenge posed by SARSCoV-2 infection and its variants?The findings of Bowen et al.(1) and Noé et al.(4) have offered us new insights into the actual repercussions of SARSCoV-2 virus infections on public health. They unmistakably point to the late sequelae and complications arising as secondary effects of the viral infection, causing severe and long-term damage to global public health. Rather than the acute infection which has a very low mortality rate in the general population, as initially and commonly believed.

Keywords: SARSCoV-2 Virus, Long Covid, Spike Protein, Long Term Covid Complications.

1. Main Text

The SARSCoV2 coronavirus, whose origins have been debated, has given rise to numerous variants that have infected a staggering 676,609,955 individuals globally as of the time of writing. SARSCoV2 exhibits a remarkable capacity for rapid dissemination, high contagiousness, and frequent mutations, particularly in the Spike protein, which plays a pivotal role in binding to the ACE2 cell receptor, facilitating cell entry, and replication. Recent studies have raised concerns about the effectiveness of Covid-19 vaccines in preventing reinfection or viral spread. Additionally, there is ongoing controversy regarding the extent to which mRNA vaccines reduce mortality associated with Covid-19. Fortunately, it is now well-established that while SARSCoV-2 and its variants are highly contagious, they are associated with relatively low mortality rates. Thus, the current COVID mortality rate by age is:

0-19 years old 0.0003%
20-29 0.002%
30-39 0.011%
40-49 0.035%
50-59 0.123%

This underscores that the acute SARSCoV-2 infection, on its own, does not constitute a significant public health concern.

What has been truly serious and devastating is the collective panic generated by health authorities (WHO, UN, NIH, FDA, CDC, EU, etc.) and by the mainstream corporate media, which disseminated often inaccurate 'official' information while censoring independent, now proven accurate, sources. This state of affairs resulted in drastic measures such as lockdowns, business closures, work stoppages, and school shutdowns, inflicting significant harm on the economy, education, and mental health, ranging from anxiety to suicide, for many individuals.

The collective considerations presented here lead to a crucial question: What truly constitutes the primary public health challenge posed by SARSCoV-2 infection and its variants? More than 3 years after the start of the global COVID-19 pandemic, a wave of evidence suggests that infection with coronavirus 2 (SARS-CoV-2), can cause post-acute sequelae in pulmonary and in a wide range of extrapulmonary organ systems, including increased risks and burdens of cardiovascular disorders, neurological and mental health disorders, metabolic disorders (diabetes and lipids disorders), renal disorders, and gastrointestinal disorders. According to estimates, 1 in 20 citizens in EEUU may have post-acute sequelae (also known as Long Covid). The risks and burdens of these sequelae have been assessed within a few months to a year after the onset of infection. Few studies with longer follow-ups (more than 1 year) examined a limited set of symptoms in people with COVID-19 or focused exclusively on neurological sequelae.

It was not yet clear if, and over what time horizon, the risk of post-acute sequelae of SARS-CoV-2 abates and is no longer significant. A comprehensive assessment of the risks and burden of post-acute sequelae of COVID-19 (PASC) in acute infection care settings within 2 years of infection or longer was not yet available. Addressing this knowledge gap would deepen our understanding of the post-acute and long-term health trajectories of people who had SARS-CoV-2 infection and inform post-COVID care strategies. Two recent outstanding and valuable papers shedding light on SARSCoV-2 infection and its variants

has been published. They undoubtedly provide much-needed clarity regarding the actual consequences of SARSCoV-2 infection.

In their remarkable study Bowe et al., used the US Department of Veterans Affairs (VA) national health care databases to create a cohort that included 138,818 people with COVID-19 and 5,985,227 people with no known SARS-CoV-2 infection, estimated the risks of postacute death, hospitalization, and a full range of 80 prespecified sequelae over five pre-specified time periods and cumulatively over 2 years [1]. The findings show that among people who were not hospitalized during the acute phase of SARS-CoV-2 infection (this group represents the majority of people with COVID-19), the risk of death ceases to be statistically significant at 6 months (possible risk horizon range: 3 to 12 months) after infection and the risk of hospitalization remains elevated up to 19 months (12 to 24 months) after infection. The risks of both death and hospitalization remained statistically significantly elevated during the 2year follow-up in those who had been hospitalized during the acute phase of SARS-CoV-2 infection. At 2 years, the risks of sequelae remained elevated for 31% and 65% in non-hospitalized and hospitalized individuals, respectively. In total, 2 years after SARSCoV-2 infection, PASC contributed 80.4 DALYs per 1,000 people among the non-hospitalized and 642.8 DALYs per 1,000 people among the hospitalized. Although most of the DALYs came from the first year after infection, a considerable proportion (25.3% in those not hospitalized and 21.3% in those hospitalized) were from the second year. Overall, the findings show that while the risks of many (but not all) post-acute sequelae decline and become non-statistically significant over time, the decline is less pronounced among those who were hospitalized in the acute phase of the infection. The findings highlight the significant cumulative burden of health loss due to PASC and call for attention to the care needs of people with long-term health effects due to SARS-CoV-2.

Among the non-hospitalized group, the risks of 24 sequelae (of 77) remained elevated, including several gastrointestinal, musculoskeletal, and neurologic sequelae, suggesting a longer risk horizon for these organ systems. Among those hospitalized, the risks of death, hospitalization, and 50 sequelae (of 77) representing each organ system remained statistically significantly elevated at 2 years, suggesting the difficult and lengthy road to recovery among those whose illness it was severe enough to require hospitalization during the acute period. Taken together, the findings suggest that the risk horizon for post-acute sequelae after SARSCoV-2 infection is prolonged even among nonhospitalized persons and is further prolonged among hospitalized persons. The outstanding work conducted by Bowe and colleagues provides exceptionally valuable and essential insights, leaving no doubt that the true consequences of SARSCoV-2 infection and its variants on global public health are not limited to the respiratory symptoms of acute infection, as initially believed by many [1]. Instead, the focus should be on the late complications arising from mild, moderate, or severe acute infections caused by the SARSCoV-2 virus.

Pathophysiological mechanisms responsible for these late complications, induced by the infection of SARSCoV-2 virus and its variants, are actively being investigated. It's worth noting that vaccines based on mRNA platforms such as Pfizer and Moderna have also been associated with a range of adverse reactions in vaccinated individuals, resembling those described by Bowe and colleagues and other researchers. In this context, we have previously proposed that the late complications of SARSCoV-2 infection and the severe adverse reactions associated with mRNA vaccines can largely be attributed to thrombotic vasculitis induced by the sustained and widespread expression of the SPIKE protein encoded by mRNA vaccines. Further details can be found in 'Long COVID and Serious Side Reactions to mRNA-Based Vaccines (VSITV) are Mainly Spike ProteinInduced Thrombotic Vasculitis,' published in [2,3].

The other recently published and highly significant study is that of Noé et al. [4]. The primary findings of this study in children include: (i) Pfizer vaccine administration leads to alterations in heterologous bacterial and viral cytokine responses at 28 and 182 days post the primary vaccination schedule, compared to pre-vaccination levels; (ii) the effects of Pfizer vaccination on heterologous immunity persist for viral but not bacterial stimuli; and (iii) there is no observed correlation between the heterologous immunological effects and the IgG responses to the spike protein encoded by the Pfizer mRNA vaccine. This study offers unique insights into the heterologous effects of COVID-19 vaccination in a pediatric population. This work demonstrates that, in children, vaccination with Pfizer mRNA decreases inflammatory cytokine (IFN-γ, MCP-1, IL-6, IL-8, and IL-15) responses to heterologous bacterial, fungal, and viral restimulation . A study in 16 adult healthcare workers reported heterologous effects of the same mRNA-based vaccine (Pfizer) used by Noé, et.al., study [4,5]. The study in adults found decreases in IFN-γ and IL-6 production after stimulation with heterologous stimulants of bacterial and viral origin and increases in inflammatory cytokine production after stimulation with C. albicans, confirming the findings of Noé and collaborators carried out in children.

Very interesting, Murphy et al. showed that ChAdOx1 nCoV-19 vaccination (vaccine containing virus inactivated on an adenovirus platform) of 10 adult volunteers was associated with increased production of IL-6, MCP-1, and IFN-γ after TLR stimulation (LPS or Pam3Csk4) and mycobacteria (M. tuberculosis) [6]. This demonstrates that the decrease in immune responses and the decrease in cytokine production to heterologous agents are unique effects of the vaccines with mRNA platforms. Vaccination with Covid mRNA in mice and humans resulted in enhanced innate immune responses, including enhanced plasma IFN-γ concentrations after the second vaccination in response to SARSCoV-2. The RIG-I/MDA5IFNAR1 signaling pathway is essential for the production of IFN-γ and other cytokines (such as IL-6, IFN-α, MCP-1, and MIP-1β), and for innate and adaptive cell activation after Pfizer mRNA vaccination in mice. Activation of this pathway results in crosstalk between cytosolic RIG-I-like receptor and membrane-bound Toll-like receptor signaling, and increased susceptibility to respiratory disease in viral and bacterial coinfections. A possible mechanism for the decreased

heterologous cytokine responses after vaccination with mRNA vaccines observed in the study by Noé et al., is the interference of the RIG-I/MDA5-IFNAR1 pathway induced by the mRNA vaccine in the immune mediated responses by pattern recognition receptors to heterologous ligands [4]. COVID-19 mRNA-based vaccines have been shown to modulate transcriptional profiles in innate immune cells, generating a unique mix of myeloid cells, cells that have been associated with increased resistance against heterologous viruses. The results of Noé and colleagues add to the evolving evidence that vaccination with mRNA-based vaccines reprograms both adaptive and innate immune responses [4].

Noé and colleagues tested whether or not existed any temporal associations between Covid (Pfizer) mRNA vaccination and altered heterologous effects by studying a "dose-response" relationship between vaccination with Covid Pfizer mRNA and altered heterologous effects. This was the reason behind performing the correlation analyzes between the anti-RBD IgG antibody titer and the cytokine response to heterologous stimulation. There was no consistent correlation between Covid mRNA vaccination-induced anti-RBD IgG antibody titer and cytokine responses. This may suggest that the mechanisms driving these responses may not be directly interconnected.

The findings from Noé et al. suggest that mRNA Covid vaccines can modify the immune response to other pathogens, both those causing vaccine-preventable and non-vaccine-preventable diseases [4]. This holds particular significance for children, who are exposed to a wide range of microbes through day care, school, and social activities, often encountering them for the first time. Therefore, before considering the simultaneous administration of mRNA Covid vaccines with other vaccines like the one against Influenza (currently promoted), it is imperative to conduct studies examining the clinical effects of these heterologous interactions related to mRNA COVID-19 vaccines in children.

In summary, mRNA-based Covid vaccines have been found to reduce both innate and adaptive immune responses to heterologous agents commonly found in the environment. Considering the low mortality rates associated with SARSCoV-2 and its variants in children, coupled with the potential adverse side effects of mRNAbased vaccines, it becomes difficult to make a reasonable argument for continuing the vaccination of children with vaccines utilizing mRNA platforms. One of the immediate and crucial actions stemming from the study by Bowe et al, is to emphasize the significance of minimizing the risk of SARS-CoV-2 infection, reinfection, and hospitalization [1]. This serves as a vital strategy for lowering the likelihood of late complications and long-term health impairments. The primary focus of public health policy should revolve around implementing measures to reduce the risk of postacute and long-term sequelae in individuals with SARSCoV-2 infection. To mitigate the risk of infection and transmission, it is advisable to explore new vaccine options (preferably ones not based on mRNA platforms, as discussed earlier in this article). These vaccines should undergo thorough efficacy testing to confirm their ability to prevent SARSCoV-2 infection and re-infection before widespread deployment, offering a strategic means to reduce long-term health issues in populations. Additionally, the promotion of effective virucidal treatments with well-documented efficacy and safety, such as La Tripleta and others yet to be discovered, coupled with global accessibility, can significantly alleviate the burden of health loss and help mitigate some of the long-term complications associated with SARS-CoV-2 infection [7].

Measures to reduce the risk of post-acute and long-term sequelae in people with SARS-CoV-2 infection should be the main basis of public health policy. Reducing the risk of infection and transmission with new vaccines (preferably NOT based on mRNA platforms due to what was previously stated in this article) whose efficacy in preventing SARSCoV-2 infection and re-infection is confirmed prior to their massive use, can be a fundamental strategic way to reduce the risk of loss of health for long term in populations. The use of effective virucidal treatments whose efficacy and safety have been well documented such as La Tripleta and others to be discovered, in addition to facilitating access to them throughout the world, can also go a long way to reduce the burden of health loss and curbing some of the longterm complications of SARS-CoV-2 infection [7].

For those who have already been affected with the late complications of the SARSCoV-2 virus, the results of Bowen et al., which provide a temporal characterization of the risks and burdens of 80 sequelae across all organ systems, may be useful in informing care pathways (ie what care people may need and at what point in their disease trajectory); and health system capacity planning [1]. The findings must also be interpreted within the broader body of evidence that has accumulated on the post-acute and long-term effects of SARS-CoV-2 on health. Recently, in addition to proposing that late complications of SARSCoV-2 infection and severe reactions to mRNAbased vaccines are primarily attributed to thrombotic vasculitis, we have also recommended a rational treatment protocol for these complications. This protocol involves the combined use of corticosteroids, anticoagulants, anti-platelet agents, and mTOR inhibitors[2,3]

It is clear that the burden of health loss will not only affect patients and their quality of life, but also potentially contribute to a decline in life expectancy and may affect labor participation, economic productivity, and social well-being. The findings that SARS-CoV-2 causes post-acute and longterm health effects need to be framed in the broader context of infection-associated chronic disease: that infections (viral and non-viral) can cause post-acute and chronic disease and that there is likely to be a two-way link between noncommunicable diseases and infectious diseases, in that noncommunicable diseases often increase the risk of infection and adverse outcomes after infection, and that a viral infection can lead to the emergence of newly emerging noncommunicable diseases. The findings of Bowen et al., and Noé et al., have offered us new insights into the actual repercussions of SARSCoV-2 virus infections on public health [1,4]. They unmistakably point to the late sequelae and

complications arising as secondary effects of the viral infection, causing severe and long-term damage to global public health. Rather than the acute infection which has a very low mortality rate in the general population, as initially and commonly believed.

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