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Perspective

Covid-19 and Immunity in Aging Populations — A New Research Agenda

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The race is on throughout the world to develop Covid-19 vaccines and therapeutics and end a pandemic that threatens to infect a substantial portion of the planet's population and perhaps kill millions of people, especially older adults. As billions of dollars flow into research and development efforts aimed at controlling the virus, the pandemic response remains hamstrung by our limited understanding of how to generate effective immunity, particularly in the elderly.

As we age, health conditions associated with aging, particularly noncommunicable diseases such as heart disease, cancers, and metabolic and autoimmune diseases, combined with treatments for these diseases and with immune senescence, substantially affect responses to vaccines and infectious diseases.[1] Angiotensin-converting enzyme 2 (ACE2) has been identified as the receptor for SARS-CoV-2, the virus that causes Covid-19, and it has been suggested that differential levels of ACE2 in the cardiac and pulmonary tissues of younger versus older adults may be at least partially responsible for the spectrum of disease virulence observed among patients with Covid-19. These findings have led to debate regarding the potential use of ACE inhibitors in the context of the pandemic.[2] This idea highlights the need for longitudinal studies in aging populations — such as the Rotterdam Study (a prospective cohort study focused on cardiovascular, neurologic, ophthalmologic, and endocrine diseases) — to examine the impact of coexisting conditions and therapies on the effects of vaccines and infectious diseases.

Even as the brunt of severe illness from Covid-19 is being borne by aging adults, we are navigating partially blind in efforts to develop vaccines and therapies to stop this and future pandemics, since we lack knowledge of the mechanisms of immunity to protect this population. If we can delineate principles of effective immunity in the elderly, we might also be able to develop new strategies for broader disease prevention and control in older populations.

Covid-19 has highlighted the vulnerability of aging populations to emerging diseases. This susceptibility to disease and death is also a major challenge for the development of vaccines and immunotherapeutic agents. Numerous studies have shown that vaccine efficacy decreases significantly with age, a reduction that is thought to be driven by the progressive age-related decline of innate and adaptive immune responses.[3] Yet we know that some

older people are protected by generally poorly performing vaccines, and some vaccines work very well in elderly populations: the Shingrix vaccine for shingles, for example, is 90% effective in people over 70. What accounts for the variability in immune responses from one elderly person to another? How can we use our understanding of this variability in developing new and improved vaccines and therapies?

Far from being mere academic exercises, the answers to these questions are critical to the future of global health. The Covid-19 experience in aging populations offers a window into the profound, long-term, global demographic challenges the world is facing. According to the United Nations, projections indicate that by 2050 there will be more than twice as many people over 65 as there are children under 5, and the number of people 65 years of age or older globally will surpass the number of people 15 to 24 years of age.[4]

This global aging will create widespread public health challenges, dramatically increasing the burden of noncommunicable diseases and exposing our vulnerability to infectious diseases. The number of deaths related to antimicrobial resistance is projected to reach 10 million per year by 2050, exceeding mortality from cancer. Climate change could put an additional 1 billion people at risk from tropical vectorborne diseases, and potentially pandemic diseases are emerging with greater frequency. Protecting aging populations will be a central, if not the primary, question in maintaining global health and biosecurity.

Recent technological advances in biomedical and computer sciences provide an unprecedented opportunity to decode the human immune system. Innovations in systems biology applied in clinical immunology studies now allow immensely detailed measurements of human transcriptomic, proteomic, immune, and metabolic responses. Such studies have already led to improved understanding of the extent to which human responses within a population vary on several parameters, and of the influence of the microbiome in host immunity, leading to considerations for novel vaccination and immune-therapeutic strategies.[5] For example, many baseline "omic" signatures predictive of vaccine-induced immunity have been associated with innate immune parameters, which suggests that specific and novel immunomodulators may enhance future vaccines and immunotherapies.

Moreover, advances in bioinformatics, causal inference, and artificial intelligence (AI) — building on AI advances from other fields, such as biomedical imaging — enable analyses of large-scale data sets that can help in determining the key elements and principles of effective human immunity. These tools offer the potential for elucidating the mechanisms that differentiate people who have a response to vaccines from those who do not, and for clarifying why some people develop effective immune responses to disease. These answers should provide the basis for accelerating the discovery and development of new vaccines, diagnostics, and therapies for major diseases. Generating systems-biology data on an unprecedented scale should also enable computational scientists to begin to develop AI models of human immunity, which, if successful, could transform product development, enabling computer-generated simulation trials to facilitate faster and cheaper development, with a much greater probability of success.

Innovative new studies are needed to investigate questions of why some people have stronger responses to vaccines or diseases than others so that we can better prevent and treat disease. This undertaking will require a global approach and a radically new vision — one that spans diseases and sectors of society, bringing together academia, industry, government, and philanthropic organizations. Covid-19 is already catalyzing collaboration among these sectors, and this work must continue beyond the pandemic.

Thus, the tools are now available to decipher the principles of effective immunity in aging populations. If investigators study cohorts of elderly people longitudinally and globally and probe their immune systems with licensed vaccines to distinguish people with effective responses from those without, and apply cutting-edge tools from systems biology and AI, it should be feasible to identify biomarkers for effective immunity in this population, which could then be applied to other vulnerable populations, such as those living in low- and middle-income countries. Over the long term, the research agenda will need to include cultivation of a new generation of multidisciplinary scientists trained in biomedical, informatics, and computer sciences in order to fully prepare for the next wave of emerging diseases.

Covid-19 is highly transmissible, causes relatively high mortality, particularly in aging popula-

tions, and has emerged globally in our highly interconnected world. Short-term efforts to quickly develop lifesaving vaccines and therapeutics are of the utmost importance.

In the long term, however, we will have to shift from investing primarily in disease-specific research to simultaneously targeting sufficient resources toward decoding the human immune system, particularly for the world's most vulnerable populations. Such an effort could accelerate the development of new vaccines, diagnostics, and treatments — not just for Covid-19, but also for future emerging pathogens as well as the noncommunicable diseases of aging that are our major global killers. We need bold action as soon as possible to help all of humanity live longer and healthier lives.

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