Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Vaccine-induced protection in aging adults and pandemic response

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A wide range of studies have demonstrated that human immunity can vary significantly across demographics. In particular age-associated declines of the immune system in older adults known as immunosenescence has become an increasingly important field of study. The impact of aging on immunity is associated with an enhanced susceptibility to both infectious and non-communicable diseases, and a substantial increase in disease severity and mortality. Immunosenescence can also limit the effectiveness of vaccines.

The concept of immunosenescence is particularly relevant within the context of the COVID-19 pandemic. Age is one of the biggest risk factors for severe disease and mortality associated with SARS-CoV-2 infection, and the question of whether COVID-19 vaccines will work as well in the older adults remains an open question. Given the rapidly aging world population and the threat from both current and future pandemics, new approaches to elucidate the dynamics of immunosenescence, as well as strategies for designing vaccines that more effectively protect older adults are both urgently needed.

Understanding immune age and its consequences

The global population of aging adults is rapidly increasing, largely as a result of improved public health strategies that have extended life expectancy. There are now an estimated 790 million individuals over the age of 65 worldwide, and that number is projected to increase to 1.5 billion by 2050, at which point adults over 65 would comprise one-sixth of the global population. This represents one of largest demographic shifts in human history. One of the implications of this shift is that there is a growing global burden of both non-communicable and infectious diseases.

Underlying the chronological aging of the population is a biological and even immunological age that affects how the body responds to disease. The decline of the immune system is characterized by increased and progressive dysfunction and deterioration of immune function, including changes in the composition, frequency, and function of innate immune cell types, as well as limited diversity within B and T cell receptors, the chronic production of cytokines leading to a continuous state of inflammation that is associated with disorganized disease response, and age-related changes in primary lymphoid organs [1,2]. Data from the current COVID-19 pandemic demonstrate substantial variation in population-based severity of disease, with age being a significant risk factorfor symptomatic infection, hospitalization, critical illness, and death. The immunosenescence that occurs as the immune system ages, and the dysfunction associated with this, plays a significant role in COVID-19 disease severity in older adults [3], as do many of the comorbidities that are also risk factors for COVID-19 severity and mortality. Recent data from the US Centers for Disease Control and Prevention show that adults aged 65–74 years are 90 times more likely to die from COVID-19 than 18–29 year olds, while those over 85 years old are 630 times more likely to die [4].

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Immunosenescence has also been associated with limiting vaccine effectiveness, including for hepatitis B [5], pneumococcal [6], and influenza [7] vaccines, among others. Various studies have provided evidence that antibody titers and antibody quality are both diminished in older adults as compared to younger adults [8]. However, this is not true for all vaccines. Vaccines that are more effective in older adults utilize several strategies including: 1) altering the route of administration, for example using intradermal administration of inactivated influenza vaccines [9]; 2) increasing the dose of vaccine, which is also used for inactivated influenza vaccines [10], and 3) using vaccine adjuvants, which is the case for the shingles vaccine. The Shingrix vaccine for shingles, which is administered with the AS01B adjuvant, has generated 90% efficacy in adults over age 70 [11], though the underlying mechanism of this augmented protection is not yet fully understood.

Implications for the current COVID-19 pandemic

The efficacy of COVID-19 vaccines among older adults worldwide will have widespread implications for disease mitigation efforts, reduction in mortality, and ultimately how fast the pandemic will be blunted or ultimately ended. Currently the World Health Organization has set the target product profile for COVID-19 vaccines as having at least 70% efficacy on a population basis with endpoint assessment based on disease, severe disease, or shedding/transmission in the preferred scenario, or 50% in the critical or minimal scenario [12]. Given high variation in demographic structures across countries, vaccine efficacy may vary geographically. Countries such as Italy and Japan have large percentages of adults over the age of 65.

Under current pandemic planning, approved COVID-19 vaccines will be rolled out initially to high-risk groups, including healthcare workers, older adults, and those with underlying conditions that put them at increased risk due to limited capabilities to manufacture enough vaccine. Effectiveness of such vaccines within older adults, as well as the as the number doses required for protection, will significantly impact how rapidly the pandemic can be controlled and eventually ended within this sub-group. Sub-group efficacy may play a critical role in determining the utility of this limited global resource.

Vaccine acceptance and uptake are also important factors in determining how quickly the pandemic will subside. Recent polling showed wide global variation in the acceptance of COVID-19 vaccines. In the US, a recent study found that vaccine efficacy was the single most important indicator of vaccine acceptance— only 61% of those surveyed indicating they would take a vaccine of 90% efficacy, with acceptance dropping as efficacy declines [13].

There are now several hundred vaccine candidates in various stages of development, with about 10 candidates currently in Phase III efficacy trials. The earliest signals of vaccine efficacy are just beginning to emerge. Questions remain about the efficacy of COVID-19 vaccines in key subpopulations such as older and elderly adults. In response to the rapidly spreading SARS-CoV-2 pandemic, vaccines were prioritized that could be rapidly developed and have progressed through the pipeline with unprecedented speed. Most of these lead vaccines however are based on vaccine platforms or approaches that have been associated with lower immunogenicity, the need for multiple doses, and more narrow immune responses [14]. Depending on the level of efficacy seen for the initial portfolio of COVID-19 vaccines, it may be necessary to reformulate or develop a next-generation of COVID-19 vaccines, particularly to protect the vulnerable subgroups of older adults and the elderly. Next generation approaches could incorporate live-attenuated vaccines, which generally provide fuller and more potent immune responses, but take longer to develop, or the use of adjuvants, dose escalation, or alternate routes of administration as mentioned above for existing vaccines.

In addition to optimizing COVID-19 vaccines for older adults, the dynamics of a rapidly aging world make it critical for additional clinical research into protecting older adults. To date, research on the aging of the immune system have had several gaps. Firstly, animal models for gauging the impact of immunosenescence are lacking. Mice have been used to understand key issues such as adaptive immunosenescence despite the fact that mice age on a very different time scale than humans, among other differences in biology and aging. Secondly, studies with human samples have largely been limited to *in vitro* studies and not more predictive *in vivo* studies [15]. Finally, new tools, including the advances in systems biology, have yet to be applied fully to the study of immunosenescence. These tools offer the potential to broaden the understanding of differences between older and younger populations, and look at immune responses across the body. Longitudinal studies remain the gold standard for life course studies, and when combined with a systems biology approach would offer scientists the opportunity to unravel the underlying dynamics of immune aging, as well as interventions to improve disease outcomes and vaccine effectiveness in older adults [16].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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