



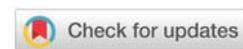
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Mini-Review

COVID-19 vaccines in elderly subjects: Considerations on efficacy and safety

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Introduction

The SARS-CoV-2 pandemic dramatically involved elderly subjects, causing a very high number of deaths in this specific population, with a risk of mortality reaching 50% in subjects older than 80 years [1-3]. As a consequence, as the world prepares for a mass campaign to vaccinate as many people as possible in the shortest time, older and frailty individuals have been recognized as categories to be vaccinated first. Several countries assessed that it was mandatory to work on vaccine campaigns in these groups of patients, therefore elderly patients and residents in care homes were among the first group of individuals to be vaccinated [4]. But what is the evidence that the vaccines are safe and effective in this population? This paper reviews the vaccine currently available, with a particular focus on the evidence of their safety and efficacy in the older population.

Vaccines in the elderly

The efficacy of vaccines in general in older people is not well studied [5]. Usually, the measurement of efficacy is based on surrogate markers as antibody titers, antibody isotypes and the ability of the immune system to neutralize pathogens. Immune-senescence is a broad term used to describe the declining immunity with age, including both quantitative and qualitative aspects of immune system responses that are likely to impact on the safety and efficacy profile of vaccines. Advanced age is associated with a natural reduction in naive T cells available to respond to a vaccine. The normal ratio of CD4:CD8 cells becomes much higher in elderly individuals, due to a significant decrease in CD8 T cells. Ageing also brings a loss of T cell receptor diversity in both CD8 and CD4 cells, leading to an overall reduced T cell survival. Further, qualitative changes in the immune response are also present,

as the production of short-lived effector T cells over memory precursor cells, resulting in an impaired response of T follicular helper cells to vaccination. Naive T cells are also genetically and phenotypically more alike to central memory T cells than they are in a younger population, impacting their plasticity [5]; B cell number remains more consistent with age but, due to a reduced expression of select proteins in old age, fewer functional antibodies are usually produced [6]. The evidences from preliminary data on COVID-19 infection indicate that both humoral and cellular adaptive immunity mediate the immunological protection towards such an infection, therefore an effective vaccine should induce both of them [7]. As a consequence, vaccines are likely to be less effective in old than in young individuals. However, the relative importance of cellular aspects of the immune response in COVID-19 is still unclear, especially in elderly individuals, so antibody levels could not be an adequate surrogates for evaluating the immunity in this specific population [8]. The impact of immune-senescence on vaccine safety is even more uncertain, especially in subjects with underlying chronic diseases; both these conditions may impact the outcome of COVID-19 infection itself and also the immune response to vaccine [9]. Though the risk of serious adverse events mediated by over-activation of the immune system is theoretically lower, this may be offset by increased predisposition to adverse events overall, as this is the hallmark of frailty.

COVID-19: mRNA vaccines

The vaccines manufactured by Pfizer and Moderna are novel messenger RNA (mRNA) vaccines; initial results suggest an optimal efficacy, achieving > 90% of protection. They work by injecting mRNA encoding the SARS-CoV-2 spike protein directly into the host. Although pure mRNA is rapidly downgraded, a number of technological advances in delivery



methods and RNA carriers over the last decade allow efficient and safe uptake of mRNA into the cytosol, where ribosomes then translate the mRNA to produce a viable protein that can stimulate an immune response. The advantages of this technology over more conventional vaccine types are numerous, including better safety (as no infectious agents are involved in their production), low risk of developing mutations, lower risk of antigen degradation *in vivo*, and, finally, a very rapid mass production at lower cost, as *in vitro* reactions can rapidly generate high yields of the therapeutic agent [10]. However, very few data are currently available on safety and efficacy concerns of mRNA vaccines in elderly subjects. Recently, the phase I data of the Moderna vaccine have been published [11]; this study involved 40 patients and the antibody responses in older individuals was comparable to those seen in younger. However, this study included only 40 healthy people aged 58 or over, so the relevance and the application of these findings in the entire elderly population with frailty is questionable. Self-limiting mild to moderate adverse events were common, with all 20 participants aged 71 or over reporting local side effects such as pain at the injection site and 80% of them reporting systemic symptoms such as lethargy. Over 25% (around 8,000) participants of the Moderna phase III study are aged 65 or over and a similar proportion have chronic diseases, so the evidence base will improve once full interim results are published.

For the Pfizer BNT162b2 vaccine (Comirnaty®), data on efficacy and safety in elderly population can be extrapolated by the published results [12]. This trial enrolled over 37000 individuals that were randomized to receive vaccine or placebo. Of these individuals, more than 40% were 55 years or older. The statistical analysis showed a very high efficacy in all the population considered, regardless of the age group. In particular no subject older than 75 years developed COVID-19 infection during the follow-up, and only 1 patient developing COVID-19 infection was older than 65 years. Regarding safety, pain at the injection site was reported less frequently among participants older than 55 years (71% reported pain after the first dose; 66% after the second dose) than among younger (83% after the first dose; 78% after the second dose). Systemic events were more often reported by younger vaccine recipients (16 to 55 years of age) than by older and more often after dose 2 than after dose 1. The most commonly reported systemic events were fatigue and headache (59% and 52%, respectively, after the second dose, among younger vaccine recipients; 51% and 39% among older recipients), although fatigue and headache were also reported by many placebo recipients (23% and 24%, respectively, after the second dose, among younger vaccine recipients; 17% and 14% among older). The frequency of any severe systemic event after the first dose was 0.9% or less. Severe systemic events were reported in less than 2% of vaccine recipients after either dose, except for fatigue (in 3.8%) and headache (in 2.0%) after the second dose. Fever (temperature, $\geq 38^{\circ}\text{C}$) was reported after the second dose by 16% of younger vaccine recipients and by 11% of older recipients. Only 0.2% of vaccine recipients and 0.1% of placebo recipients had fever (temperature, 38.9 to 40°C) after the first dose, as compared with 0.8% and 0.1%, respectively, after the second dose. Taken together, these data confirmed the favorable profile of BNT162b2 vaccine according

to both efficacy and safety, also in individuals older than 55 years. However, no data were presented on elderly patients with significant frailty.

COVID-19: Virus vector vaccines

The vaccines developed by both the University of Oxford/AstraZeneca (ChAdOx1, Vaxzevria®) and Janssen (Ad26.COV2) are based on the genetic modification of adenoviruses that are inactivated for the deletion of the E1 gene, which is replaced with the spike gene. The Janssen Ad26.COV2 vaccine is based on a human adenovirus while the Oxford vaccine is based on a chimpanzee (ChAdOx1) adenovirus, both of which are replication defective. The choice of a chimpanzee adenovirus in the Oxford design was done to reduce the impact of human adenovirus antibodies acquired through natural exposure to human adenoviruses over time—a factor that could likely to be more important in elderly subjects. Spike protein is expressed on the virus particle surface, triggering both antibody and T cell responses that may be protective against COVID-19. Use of genetically modified organisms as vaccines dates back to the early 1980s [13] and has the theoretical advantage that the safety of the adenovirus vector at low doses is well established and likely to be transferable to new other vaccines, although the vector has never been used in large numbers of elderly individuals with frailty. Janssen's phase I-IIa trial included more than 400 healthy subjects aged 65 and over, with rates of local adverse events lower (41%) than in younger people (64%) in subjects receiving low-dose and 42% vs 78% in those receiving high-dose [14].

More robust Phase II safety data have been published for the AstraZeneca vaccine, that included 200 people aged 70 or over without severe comorbidities or frailty [15]. The vaccine was safe and well tolerated, with neutralizing antibodies developing in almost 100% of participants at 28 days follow-up across all age groups. There were no serious or unexpected adverse events and, consistent with the findings of the Janssen study, the incidence of mild and moderate severity adverse events in the immediate post-vaccination period was lower in the older age groups.

Comments and conclusions

In summary, is unusual that a vaccine program will start with older people with frailty despite scant evidence of efficacy or safety in this specific group. However, the rapidly evolving and the devastating nature of the COVID-19 pandemic in this group of individuals may justify this approach and health officials will want to avoid mistakes made during the first wave, where a policy of discharging hospitalized care home residents with COVID-19 whilst still infectious led to outbreaks and cost a large amount of lives in different countries [16–18]. Usually, older subjects are not included in clinical trials, therefore data on experimental drugs or therapies that they may benefit from may be lacking [19]. As a consequence, the real safety and efficacy of COVID-19 vaccines in this population can be demonstrated when a large proportion of elderly individuals are vaccinated. No pharmacovigilance studies have been formally proposed or announced to date. Key



information on safety and efficacy may therefore need to be acquired retrospectively through usual regulatory authority surveillance systems and epidemiological studies. Even the benefits of annual vaccination of older people against influenza are unquantified and disputed, so the same may occur with COVID-19 vaccination programs [20]. Some may argue that the inclusion of older people with frailty or complex co-morbidity would slow down the development of a working vaccine, as the risk of severe adverse events increase. However, trials in these populations are possible and judicious application of pause rules and other safety criteria could mitigate the risk of unnecessary and costly delays. Therefore, the inclusion of “real world”, older, frailty patients in vaccine clinical trials should be recommended to obtain results effectively reproducible even in the current clinical practice.

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