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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Older adults should not be omitted from inclusion in clinical trials of SARS-CoV-2 vaccines

Since December 2019, the coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 has spread worldwide, affecting millions of people and leaving hundreds of thousands dead, mostly older adults. Recently, the five main geriatric journals in the United States have joined together to produce a common text denouncing the ageism that manifested itself during the first wave of the pandemic. This text proposes four recommendations: 1) to make clinical research more inclusive for all ages, 2) to involve geriatricians and gerontologists in institutional decisions, 3) to inform policy and funding by taking into account the specific needs of vulnerable populations, and 4) to emphasize the importance of personalized approaches (adaptation of rules) for seniors, respecting autonomy, justice and charity [1].

While North America and Latin America have not yet reached the peak of the epidemic, and as Asia and Europe face the start of a second wave of infections, no medication has shown efficacy in treating or preventing infection with SARS-CoV-2. According to the World Health Organization situation report of July 30, 2020, the case fatality rate (CFR) of COVID-19 is greater than 3.9 % in the general population [2]. Nevertheless, it covers very diverse situations between younger adults (CFR under 0.1 % in most industrialized countries) and older adults aged 70 and over (CFR from 5.6 % in the USA to a range from 38 % to 73 % for males in the nursing home population of Belgium). The susceptibility to infection in individuals under 20 years of age is approximately half that of adults aged over 20 years, and clinical symptoms manifest in 21 % (95 %CI: 12–31 %) of infections in 10- to 19-year-olds, rising to 69 % (57–82 %) of infections in people aged over 70 years [3]. Therefore, there is an urgent need for a vaccine to prevent infection with SARS-CoV-2 in older adults, who are particularly likely to be infected and to have clinical expression of COVID-19.

The main stages in vaccine development are i) the exploratory phase, ii) the preclinical phase, iii) clinical development, iv) regulatory review and approval, v) manufacturing, and vi) quality control. Clinical development consists of three phases before marketing and one phase after. Phase 1, usually on a dozen healthy volunteers, aims to observe very frequent side-effects and to identify the range of doses to use. Phase 2 includes hundreds of volunteers whose characteristics (such as age and health status) are similar to those for whom the new vaccine is intended. This phase aims to determine more precisely the immune response, to define an administration schedule and to observe side-effects. Phase 3 includes thousands of volunteers and aims to assess the efficacy of the vaccine, i.e. how the vaccinated volunteers resist the disease compared to the unvaccinated. This step also makes it possible to identify rare side-effects and to define in which population group (or age group) the candidate vaccine is effective or not.

On July 31, 2020, a search of ClinicalTrials.gov performed with COVID-19 as “condition disease” and vaccine as “other term” revealed that 132 interventional studies were reported, but most excluded older adult (i.e. participants aged 70 years and over) or oldest-old adults (i.e. participants aged 80 years and over). In addition, when no age limitation was reported in the inclusion criteria, studies had exclusion criteria disqualifying *de facto* geriatric patients (e.g. a medical history that could worsen the prognosis of COVID-19 including diabetes mellitus, hypertension, chronic obstructive pulmonary disease, renal failure <80 mL/min, or cardiovascular disease, and also residing in a retirement home or other nursing facilities, or needing nursing care).

Among these studies, only four large randomized controlled trials (RCTs) (including between 2,038 and 32,000 participants depending on the RCT considered) conducted in the USA (testing BNT162b and mRNA-1273), in the UK (testing MenACWY) and in Germany (testing VPM1002) offer the possibility of including elderly participants. Enlarging the number of countries likely to participate in these RCTs and including as high a proportion of elderly participants as possible in SARS-CoV-2 vaccination RCTs is however essential.

The main reason is of course the fact that older adults are the most able to benefit from a vaccine, with significant benefits expected in terms of public health, given their higher risk of a pejorative evolution of COVID19 and death. In itself, this characteristic is also a statistical argument for the feasibility of clinical trials because older adults have a higher probability of health events [3], which makes it possible either to reduce the size of the studied sample or to reduce the follow-up duration. Another reason for testing vaccines in older adults is precisely the one that led previous RCTs to avoid including them, namely the specificities that make older adults different from middle-aged adults. First, older adults exhibit an altered immune response - called "immunosenescence" - which is generally associated with poor vaccine response and makes it difficult to extrapolate the effective dose of vaccine from data collected in younger adults [4]. Second, they present with a modified expression of COVID-19 from younger adults, with clinical signs that are different, few in number and non-specific [5]. Third, they accumulate chronic diseases, which are added to COVID-19, often with functional consequences such as loss of autonomy and independence; they have different social characteristics marked by isolation or on the contrary by the need for professional help for the activities of daily living. Fourth, some are qualified as frail when their precarious state of health is at risk of decline at the slightest stress, for example due to the COVID-19 whether in its severe but also mild form. All these elements explain why the designers of RCTs generally prefer not to include older adults in RCTs, including during the COVID-19 era; whereas it appears to us, on the contrary, crucial to include older adults in large RCTs or to offer them dedicated trials to better understand COVID-19 and discover an

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effective and safe vaccine in this very special population. Older adults are our past and, for the lucky ones of us, our future. We should seize together this opportunity to secure our future.

Contributors

Guillaume Sacco drafted the manuscript.

Thomas Célarier critically revised the manuscript for important intellectual content.

Gaetan Gavazzi critically revised the manuscript for important intellectual content.

Cédric Annweiler drafted the manuscript.

Conflict of interest

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