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.

Vaccine 39 (2021) 2325–2327

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Commentary

Are vaccines against COVID-19 tailored to the most vulnerable people?

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The rapidly growing evidence that different vaccines are effective against coronavirus disease 2019 (COVID-19) arouses hope that most of at-risk population will be immunized within the current year. Despite the well-known age-related immunological changes [1], trials' results suggest that COVID-19 vaccines might achieve comparable efficacy in younger and older adults, the latter being the most vulnerable to the disease.

About recommended inclusion criteria that make Clinical Trials results applicable to the general population, the ICH E7 2009 Q&A revision [2] reaffirms the need for a meaningful representation of age classes over 65 years, and particularly those over 75 years. Ideally, the age distribution in the tested population should mirror the incidence of the target disease in the general population. Increased attention to involving older adults in confirmatory clinical trials has been paid in the last decade, including initiatives to develop adapted formulations e.g. a high-dose anti-flu vaccine by Sanofi [3], not made available in the EU.

Table 1 summarizes the health-related eligibility criteria for participation in the experimental phases 2–3 clinical trials on COVID-19 vaccines developed by Pfizer/BionTech, Moderna, and Oxford-AstraZeneca.

Pfizer/BionTech included healthy participants, but chronic diseases could lead to the proband's exclusion based on the investigator's judgment in the absence of any structured selection process. Of interest, there were no upper limits for age [4]. As reported in the paper of Polack et al., 42.2% of participants were >55 years of age, but only around 4.4% were aged ≥75 years [4]. The vaccine efficacy seemed to be consistent across people of different age, gender, and ethnicity, and in individuals aged ≥65 years, it was over 94%.

In Moderna's phase 3 trial, adults either healthy or with stable chronic diseases were tested, while immunocompromised states were excluded. Also in this case, no upper limits of age were posed [5]. Of the total COVID-19 incident cases observed in the placebo and the mRNA-1273 groups, 16.8% were aged 65 years or older [5]. The trial results reported a vaccine efficacy of 94.1%, and the estimate for the age category ≥65 years was 86.4% [5].

Stricter inclusion and exclusion criteria were set in the clinical trial Oxford-AstraZeneca [6,7]. Indeed, the trial included healthy adults or individuals with mild or moderate and well-controlled diseases, as evaluated by the investigator. Among the exclusion criteria, there were several clinical conditions that are very common in advanced age, including but not limited to cognitive impairment, dementia, and frailty, which is a primary risk factor for death in COVID-19 patients [8]. Importantly, individuals with a Clinical Frailty Scale of 4 or higher were excluded from the trial. As shown in Table 1, despite a substantial involvement of older individuals in the primary immunogenicity and reactogenicity analysis [6], the proportion of participants in advanced age in the four-sites interim analysis [7] was much lower.

Concerning the reactogenicity and immune response to the vaccines mentioned above, older individuals demonstrated fewer local and systemic reactions [4–6] and similar immunogenicity rates in terms of antibody and T-cell responses [6,9,10], compared to younger participants.

Overall, although older persons are quite well represented in these confirmatory clinical trials on COVID-19 vaccines, it looks like that the most vulnerable older people, including frail and multimorbid individuals and long-term care facilities residents, have

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https://doi.org/10.1016/j.vaccine.2021.03.066

Table 1
Health-related eligibility criteria influencing geriatric representation in the clinical trials for vaccines against COVID-19.

	Pfizer/BionTech [4]	Moderna [5]	Oxford-AstraZeneca [7]
Age classes	42.2% with age > 55 years	24.8% with age ≥65 years	15.9% with age >55 year (10.9% from 56 to 70 years, and 5% >70 years)
Inclusion criteria	- Healthy participants who, through medical history, physical examination, and clinical judgment of the investigator are eligible for inclusion in the study. - Individuals with preexisting stable disease (i.e. disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment).	Healthy adults or adults with pre-existing medical conditions who are in stable condition (i.e. not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrollment).	Healthy adults or adults with comorbidities assessed as mild or moderate and well controlled by the Investigator.
Exclusion criteria	- Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study. - Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.	- Acute illness or fever 72 h prior to or at screening. - Immunosuppressive or immunodeficient state.	- Severe or uncontrolled conditions, e.g. cardiovascular, respiratory, gastrointestinal, liver, renal diseases, endocrine, autoimmune/ rheumatological disorders, neurological illness, immunosuppression, and cancer. - Chronic use of anticoagulants. - Psychiatric conditions (including dementia or cognitive impairment), or psychiatric history. - Any other comorbidities deemed severe or uncontrolled as determined by the clinical judgement of the Investigator. In case of uncertainty regarding the nature or severity of the comorbidity (e.g. new medical diagnosis; new symptom, disorder or finding that are currently under investigation; recent change or deterioration in a symptom, disorder or finding) the participant may be excluded, at the discretion of the investigator. - Clinical Frailty Scale ≥4 (vulnerable and frail), only for participants aged ≥65 years.

not been adequately considered. Indeed, the experience of geriatric networks, such as GeroCovid Observational, a multicenter and multisetting European study [11], suggests that the real-life at-risk population of older adults with COVID-19 is characterized by a high prevalence of multimorbidity, including minor and major neurocognitive disorders, and frailty. Such studies may be useful to discuss the applicability of vaccines' experimental results to the general population. For instance, in the GeroCovid acute wards setting (**eTable 1**), the mean age of deceased COVID-19 inpatients was 81.5 ± 8.1 years and selected negative prognostic factors, like cardiovascular diseases, were highly prevalent [12]. Unsurprisingly, two-thirds of deaths concerned multimorbid patients, and results are expected to be even more marked in the long-term care facilities. These preliminary data suggest that the older population tested in some vaccine trials might not fit the older population dying from COVID-19. The efficacy, safety, and immunogenicity of COVID-19 vaccines should therefore also be investigated in this most vulnerable subgroup of people.

In conclusion, the pharmaceutical industry and upstream regulatory agencies should support and pursue a real-life validation of vaccines against COVID-19 in the most at-risk population. To the current state, it is therefore essential to monitor the effectiveness, safety, and immunogenicity of COVID-19 vaccines in the most vulnerable categories, including the frailest ones as well as patients with cancer, immunodepression, chronic degenerative diseases, or developmental disabilities. Accordingly, some multicentre initiatives, such as GeroCovid Vax [13], are monitoring vaccinated nursing home residents over time and will provide reliable information on shorter and longer-term safety and efficacy of COVID-19 vaccines in such vulnerable population.

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.

Acknowledgements

We are thankful to the colleagues of the GeroCovid Working Group who are collaborating in data collection for their valuable contribution, and to all the study participants.

Authors' contribution

All authors attest they meet the ICMJE criteria for authorship.

Funding source

None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.03.066.

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