Title

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Journal

British Journal of Clinical Pharmacology, 87(9)

ISSN

0306-5251

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Publication Date

2021-09-01

DOI

10.1111/bcp.14967

Peer reviewed

Development, evaluation and use of COVID-19 vaccines in older adults: preliminary principles for the pandemic and beyond

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No funding was received to support this commentary.

SH conceptualised and drafted the manuscript. All authors provided critical review and ideas for the manuscript. All authors edited drafts and approved the final manuscript.

The authors have no conflicts of interest relevant to this manuscript.

Development, evaluation and use of COVID-19 vaccines in older adults: preliminary principles for the pandemic and beyond

The COVID-19 pandemic brought development, evaluation and use of vaccines for older adults into the spotlight. Here, we reflect on the gaps that were highlighted and strategies to fill them, during the pandemic and beyond. This commentary draws on principles we compiled through the geriatric pharmacology subcommittee of the clinical division of the International Union of Basic and Clinical Pharmacology (IUPHAR), to guide the regulation and use of the COVID-19 vaccines for older adults.[1] They are based on principles for evaluation and use of other therapeutics in older people.

During a pandemic, regulatory and clinical decisions may need to be made rapidly and sometimes in the absence of clinical data from all at risk subsets of the population. In adults aged over 65 years, there is a wide range of physiological and pharmacological variability that needs to be considered. The increase in morbidity and mortality seen in older adults is comparable to that seen with other conditions [2], probably related to underlying biological mechanisms of ageing, physiological factors such as altered immunity, frailty (loss of physiologic reserve), altered presentation of infection, pre-existing multimorbidity, polypharmacy and nutritional deficits [3]. How these factors affect the safety or efficacy of a new drug or vaccine is not well understood.

Outcomes of COVID-19 vaccines prioritised by older patients may include more social interactions; or less severe disease, avoiding the need for hospitalisation and potentially reducing the functional impairment often seen after severe infections in older people. Public health, in turn, may prioritise reduced transmission among older adults and particularly those in residential aged care facilities. Clinically, competing risks for morbidity and mortality must be considered when deciding on vaccinations and other treatments. For people in the last weeks or months of life, enduring the side-effects of a vaccine may not seem worthwhile, since the vaccine in such cases is unlikely to reduce

hospitalisation or extend life. However, patient experiences of hospitalisation and mortality may differ when these events are caused by COVID-19, which often causes severe dyspnoea, isolation and delirium, compared to when they result from sudden vascular events or slower degenerative disease. Moreover, vaccination may allow for more social contacts with family, friends and/or professional caregivers, and thus be of particular importance during the last weeks or months of life.

Here, we outline key considerations for evaluation and use of COVID-19 vaccines in older adults and reflect on their current and potential future implementation. This includes assessment of preclinical data in aged animals and clinical data in older adults, judicious extrapolation from relevant data in younger age groups or from comparable interventions, and planning pharmacovigilance.

Ideally, direct data from preclinical models and clinical trial participants representative of the population who will use the vaccine would be available for regulatory evaluation. Preclinical data should include evaluation in aged animals to understand the effects of ageing physiology and comorbidities on immune response, efficacy and safety. There is a need for animal models that are relevant to humans, including the need for models of ageing, multimorbidity, and frailty [4]. Assessment of vaccine efficacy in such models must consider susceptibility to infection as well as clinically relevant measures of response [5]. There is a need for access to colonies of aged animals to rapidly assess effects of new treatments in old age.

At every phase, clinical trials should adequately represent older adults across the older age span in proportion to the numbers having a condition or at risk for the disease or having severe outcomes. This may include analysis of subgroups by chronologic age (65-74, 75-84 and >85 years) and of people with frailty, multimorbidity and polypharmacy. There have been deliberate efforts to study COVID-19 vaccine efficacy and safety in different age groups. However, delays in obtaining data

from older participants delayed regulatory approval of some vaccines for older adults and even resulted in contradictory recommendations by different authorities.

In clinical trials, it is important to measure clinical efficacy and safety outcomes in older adults. Clinical efficacy outcomes include prevention of infection of any severity, of symptomatic disease and of severe disease. For the very old, outcomes such as quality of life and freedom to be with other people are also highly relevant. Surrogate efficacy outcomes, or correlates of protection, such as immunogenicity, need to be interpreted in the light of known age-related changes in immune response [6]. Standard immune biomarkers, such as antibody titres, do not capture the age-related reduction in T-cell function that can impair vaccine efficacy. Clinical safety outcomes to measure include specific adverse events (which may be under-recognised and have worse outcomes in older adults), geriatric syndromes (e.g., falls, delirium) and global health outcomes (e.g., hospitalisation and mortality). While clinical trials data used to make regulatory decisions on COVID-19 vaccines suggested a lower risk of immune mediated adverse effects in old age, it is important to interpret this in view of the non-specific presentations and under-recognition of adverse effects in older people.

In the absence of adequate direct clinical trial data from older adults, regulatory and clinical decisions can be informed by extrapolation of data from younger participants and from older participants receiving comparable interventions. Extrapolation of clinical data from trials in young and middle-aged adults should consider age related changes in pharmacokinetics and pharmacodynamics, as well as the effects of the high prevalence of multimorbidity, polypharmacy and other vaccines, which can affect vaccine response and disease severity. It is difficult to extrapolate from data on responses of frail, older participants to other vaccines, particularly vaccines that use different technologies (e.g., influenza, pneumococcal, varicella-zoster [7]).

Pharmacovigilance plans should include adverse events, geriatric syndromes and global health outcomes stratified by age group, frailty and residence in a nursing home. Active surveillance is preferred to spontaneous reporting because adverse events are often under-recognised, due to cognitive impairment and non-specific presentations. Case finding and assessment of causality are complicated when assessing adverse events following immunisation (AEFI) in multimorbid and polymedicated older people. For example, the Brighton Collaboration current interim definition for case finding of thrombocytopenia thrombosis syndrome [8] requires low platelets and presence of venous or arterial thrombosis/thromboembolism, all of which are common and multifactorial in older people. For causality assessment, if the answer to the first criterion in the WHO guidelines for assessment of AEFI [9], 'Is there strong evidence for other causes', is 'Yes', as it may often be in older people who have a multifactorial increased risk of many adverse events, then the AEFI is classified as 'Inconsistent causal association to immunisation' (coincidental). Future work could develop and validate case finding and causality assessments for older adults.

In clinical decision-making about use of vaccines, it is important to consider the goals and experience of the older person. Age is only one of many factors that informs clinical decision making for populations and individuals. Shared decision-making guides for frail older people have been disseminated in some jurisdictions.[10] Such tools, informed by robust data from clinical trials and pharmacovigilance in frail older people, will help optimise use and outcomes of vaccines.

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