

Principles for evaluation and use of COVID-19 vaccines in older adults

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Internationally, vaccines for COVID-19 are being evaluated for use in older adults with limited collection of data from older adults and very limited data collection from frail older adults. Ideally, evaluation of safety and efficacy for older adults would be informed by data generated from an older population representative of the real world older adult users, across the agespan from 65 to 100 years, including those living with frailty, multi-morbidity and polypharmacy. Safety and efficacy evaluations should include geriatric outcomes such as falls and delirium that are under-recognised and under-reported through spontaneous adverse event reporting, in addition to universal outcomes of hospitalisations and mortality.

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. However, in adults over the age of 65 years there is a wide range of physiologic variability that needs to be considered in the evaluation process. The highest morbidity and mortality rates are often observed in older adults but the mechanism is not known. Contributing factors may be not only chronological age, but also physiologic factors such as altered immunity, frailty (loss of physiologic reserve), geriatric syndromes, concomitant medical conditions, concomitant medications and nutritional deficits. The interplay of these factors with the safety or efficacy of a new drug or vaccine is largely unexplored. Finally, the overall risk-benefit for new agents in older adults must include consideration of competing risks for morbidity and mortality and patient-centred outcomes and directives. Individual goals may include less isolation and reduced disease severity; while public health goals may include reduced transmission in residential aged care facilities. Patient experience of global health outcomes, such as hospitalisation and mortality, may differ between events caused by COVID-19 (severe dyspnoea, isolation) and events from other common causes.

Here, we summarise key considerations for evaluation of data on COVID-19 vaccines for use in older adults. This includes assessment of preclinical data in aged animals and clinical data in older adults, extrapolation from relevant data in younger age groups or from comparable interventions, and planning pharmacovigilance. As with other drugs and vaccines, the risk/benefit evaluation may be different for older adults when compared to younger individuals. We therefore describe some principles that should be considered in the evaluation and use of COVID-19 vaccines in geriatric patients (details in Table 1).

Optimal data to inform regulatory and clinical decision making for COVID-19 vaccines in older adults

1. Pre-clinical data should include evaluation in aged animals to understand the effects of ageing physiology on immune response, efficacy and safety.
2. At every phase, clinical trials should adequately represent older adults across the older agespan 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 age (65-74, 75-84 and >85) and of people with frailty, multi-morbidity and polypharmacy.
3. Clinical efficacy outcomes should be measured. These include efficacy to prevent infection of any severity, of symptomatic disease and of severe disease. Interpretation of surrogate efficacy outcomes, such as immunogenicity, should be interpreted in light of known age-related changes in immune response. Standard immune biomarkers, such as antibody titres, do not capture the age-related reduction in T-cell function that can impair vaccine efficacy.

4. Clinical safety outcomes that should be measured 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).

Extrapolation of data from younger participants or comparable interventions

5. 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 multi-morbidity, medications (e.g. anticoagulants, ACE inhibitors and angiotensin receptor blockers, and immunomodulators) and other vaccines (e.g. influenza vaccine), which can affect vaccine response and disease severity.
6. Extrapolation of data on other vaccines in old age and frailty is uncertain, particularly with data from studies of vaccines with different technologies.

Pharmacovigilance

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.

Clinical use of vaccines

8. The goals and experience of the older person should be considered in clinical decision making on use of vaccines. Age is only one of many factors that informs clinical decision making for populations and individuals.

Table 1. Key considerations for evaluation of data on COVID-19 vaccines for use in older adults

| Evidence | Type | Considerations for Efficacy (COVID-19 infection/disease and the surrogate outcome of immune response) | Considerations for Safety (Specific AEs, Geriatric AEs and Global Outcomes) |
|---|---|---|--|
| Pre-clinical | Studies in ageing animals | COVID-19 (subclinical to severe) Immune response | Specific AEs – e.g. fever Geriatric AEs – e.g. activity, cognition Global Outcomes – e.g. mortality |
| | Extrapolation from studies in young animals | Changes in immune response | Changes in susceptibility to AEs |
| Clinical | Clinical trials in older adults (number, age groups, frailty, comorbidities) | COVID-19 (subclinical to severe) Immune response – measure factors affected by ageing | Specific AEs from studies: prevalence, severity, resilience. Subjective AEs under-reported. Geriatric AEs – e.g. falls, delirium Global Outcomes – e.g. hospital admission, mortality |
| | Extrapolation from clinical trials in young/middle aged adults | Apply known changes in immune response in ageing and frailty to predict response | Apply known changes in susceptibility to specific and geriatric AEs and to global outcomes in ageing and frailty to predict response |
| | Extrapolation from clinical trials of other vaccines in old age (consider different vaccine technologies) | Apply changes clinical efficacy and immune response to other vaccines in ageing and frailty to predict response | Apply known changes in susceptibility to specific and geriatric AEs and to global outcomes in response to other vaccines in ageing and frailty to predict response |
| Pharmacovigilance plan for older adults (including frail) | Individual patient and population data | Prevalence of COVID-19 in those vaccinated stratified by age and frailty | Detection of specific and geriatric AEs requires objective, active measurements (less likely to recognise/ spontaneously report in old age). Include prevalence of falls, delirium, hospitalisation and mortality pre and post vaccine. |

AEs, Adverse Events