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Systematic Literatur Review

The effects of age on antibody response towards COVID-19 vaccination: A Systematic Review

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Abstract

Mortality rate of COVID-19 infection is exceptionally high in the older population. Various vaccines are being rapidly developed as an attempt to halt the pandemic. Although vaccination has been effective in reducing mortality and hospitalization rate in recent months, lower vaccine effectiveness has been reported among older adults. This review aims to evaluate and summarize current evidence on the effect of age on antibody response towards COVID-19 vaccines. Literature search was conducted on PubMed, Scopus, ScienceDirect and ProQuest for studies published up to 9th October 2022. The selected studies were assessed The Joanna Briggs critical appraisal tools. Qualitative analysis was then performed for the final studies. A final of 9 studies were included in this review. A majority of the studies evaluated the responses of BNT162b2 or mRNA-1273 vaccine, while 1 study investigated the response towards ChAdOx1 vaccine. Outcomes were measured in term of IgG antibody levels or serum neutralization. Most studies demonstrated significantly lower antibody response and neutralization in older adults compared to younger vaccinees after administration of first and second vaccine dose. However, two studies reported no significant difference in vaccine responses across age groups after third dothird-dosetration. This systematic review highlights lower immunogenicity towards COVID-19 vaccines in older population. Further research into strategies to improve vaccine responses in the elderly is required to provide sufficient protection for this vulnerable group.

Key words*: COVID-19 vaccine, antibody, neutralization, age, elderly*

Introduction

The ongoing COVID-19 pandemic has significantly threatened the global health and a subject of international concern in the recent years. As of October 2022, 615 million confirmed cases have been reported worldwide, with a total of 6.5 million deaths. (World Health Organization, 2022) Deaths may occur across all ages; however, mortality rate is exceptionally high in the older population. (Gold et al., 2020) A study by Surendra et al found that mortality rate was increased up to six-fold in COVID-19 patients ≥50 years old. (Surendra et al., 2021) Furthermore, a meta-analysis by Bonanad et al involving national registries from 5 countries revealed an exponential increase in mortality rate in patients >50 years old, with the highest mortality

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observed in ≥80 years old (Bonanad et al., 2020). These findings underscore that older patients are particularly vulnerable to severe COVID-19 infection and deaths.

Ever since SARS-CoV-2 infection was declared a public emergency, numerous efforts have been undertaken to halt the pandemic, one of which is the rapid research and development of various vaccines against the virus. The race for an effective COVID-19 vaccine gives rise to the utilization of various technology platforms to develop the vaccine. Currently, WHO-approved COVID-19 vaccine types include mRNA, protein subunit, inactivated virus, and non-replicating viral vector vaccines. (Alexandridi et al., 2022) Considering the high COVID-19 mortality rate among older population, this high-risk group is largely prioritized to receive COVID-19 vaccination in many countries (Eyal et al., 2022).

Although vaccination has been effective in reducing mortality and hospitalization rate globally, lower vaccine effectiveness has been reported among older adults. (Arregocés-Castillo et al., 2022; Lv et al., 2021) This phenomenon is largely attributed to immunosenescence, a process by which the immune system is altered with age, causing increased susceptibility to pathogens and poorer vaccine responses. (Crooke et al., 2019) Diminished vaccine responses in the elderly has been reported in several other vaccines, including influenza, pneumococcal, tetanus and diphtheria vaccines. (Pereira et al., 2020) Weaker antibody response towards COVID-19 mRNA vaccines have also been reported in older adults. (Brockman et al., 2022; Müller et al., 2021) With regard to experience from previous vaccination, questions arose as to whether older individuals also exhibit suboptimal response towards COVID-19 vaccines. This is crucial to decide whether additional strategies are required to protect this vulnerable group from the ongoing COVID-19 transmission. Therefore, this review aims to evaluate and summarize current evidence on the effect of age on antibody response towards COVID-19 vaccines.

Methods

This systematic review is conducted based on the The Preferred Reporting Items of Systematic Review and Meta-Analysis (PRISMA) Statement. Literature search was conducted on PubMed, Scopus, ScienceDirect and ProQuest databases for studies published up to 9th October 2022, using keywords and MeSH terms as displayed in Table 1. Inclusion criteria set to filter the studies was as follows: (1) clinical studies, including randomized controlled trials (RCTs), cohort and case-control studies, (2) subjects receiving COVID-19 vaccines, irrespective of vaccine types, (3) evaluate the effect of age on vaccine response, (4) studying antibody response as outcome. Conversely, non-English articles, case-reports, reviews, non-research articles, and irretrievable full-text articles were excluded.

Titles and abstracts were screened by two independent reviewers. Full-text publication were filtered in accordance with the inclusion and exclusion criteria set above. The following data was extracted from the final selected studies: author and year of publication, location of study, sample size, age, type of vaccine, number of doses, timing of antibody response measurement, and any reported outcome. The selected studies were assessed The Joanna Briggs critical appraisal tools. Critical appraisal was conducted by two independent reviewers, and any discrepancies were resolved through discussion with a third reviewer until agreement was reached between all authors. Qualitative analysis was then performed for the final studies.

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Table 1. Literature search Strategy

Database	Keywords	Filters
Pubmed	("COVID-19 Vaccines"[Mesh]) AND (("Immunoglobulins"[Mesh]) OR ("Antibodies"[Mesh])) AND (("Immunosenescence"[Mesh]) OR ("Aged"[Mesh]) OR ("Middle Aged"[Mesh]))	
ProQuest	("COVID-19 vaccine") AND (("antibody") OR ("immunoglobulin")) AND (("aged") OR ("elderly"))	"Scholarly Journals", "COVID-19 vaccines", "English", "Vaccines"
Scopus	("COVID-19 vaccine") AND (("antibody") OR ("immunoglobulin")) AND (("aged") OR ("elderly"))	"COVID-19 vaccines", "English", "Article"
ScienceDirect	("COVID-19 vaccine") AND (("antibody") OR ("immunoglobulin")) AND (("aged") OR ("elderly"))	"Research article", "Vaccine"

Study Selection

The literature search yielded a total of 2,514 initial articles, which were screened according to the eligibility criteria. After title and abstract screening and removal of irrelevant records, sixteen full-text articles were obtained and assessed thoroughly. Seven articles were then excluded for the following reasons: 1 article was a research protocol and 6 other studies lacked data on the effect of age on vaccine response. A final of 9 studies were included in our review. Details on study selection and exclusion are illustrated in **Figure 1**.

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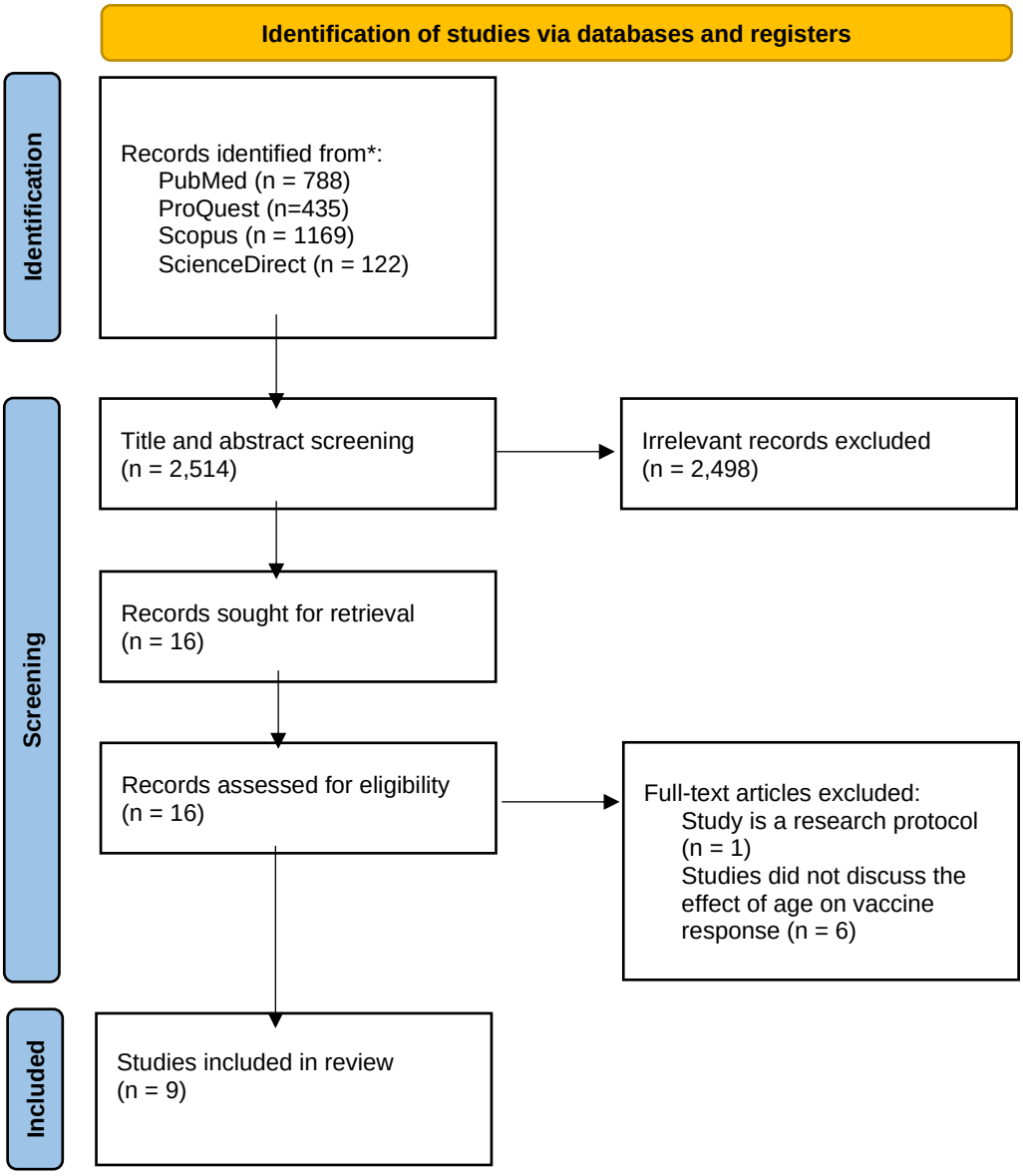

Figure 1. Flowchart of literature search and selection

Results

Characteristics of studies

The types of vaccines, timing of antibody measurement, and number of vaccine doses vary between studies. A majority of the studies evaluated the responses of BNT162b2 (Pfizer) or mRNA-1273 (Moderna) vaccine, while 1 study investigated the response towards ChAdOx1 (AztraZeneca) vaccine. Outcomes were measured in terms of IgG antibody levels or serum neutralization. Six studies evaluated vaccine responses after first and second doses, 1 study evaluated response after second dose, and 2 other studies reported on outcomes after third dose. Characteristic of each study is further detailed in Table 2. Critical appraisal of each study is detailed in Table S1.

Outcomes

To summarize, 7 studies reported lower vaccine response in older age groups in terms of anti-spike IgG or neutralizing antibody levels after administration of first and/or second dose (Table 3). (Brockman et al., 2022; Collier et al., 2021; Demaret et al., 2021; Müller et al., 2021; Mwimanzi et al., 2022; Richards et al., 2021; Vassilaki et al., 2021) However, 2 other studies by

Ramasamy et al(Ramasamy et al., 2020) and Richards et al(Richards et al., 2021) showed no significant difference in post-vaccine antibody levels between age groups after second dose with ChAdOx1 and mRNA-1273 respectively. Two studies reported no significant of age on vaccine response upon third dose administration (Eliakim-Raz et al., 2021; Mwimanzi et al., 2022).

Most studies reported vaccine response in terms of anti-spike IgG levels. (Brockman et al., 2022; Demaret et al., 2021; Eliakim-Raz et al., 2021; Müller et al., 2021; Mwimanzi et al., 2022; Ramasamy et al., 2020; Richards et al., 2021; Vassilaki et al., 2021) Six studies demonstrated significantly lower IgG levels among older groups compared to younger vaccinees after first and second doses of vaccine. (Brockman et al., 2022; Demaret et al., 2021; Müller et al., 2021; Mwimanzi et al., 2022; Richards et al., 2021; Vassilaki et al., 2021) However, age group cut-offs differ between studies. Timing of antibody measurement varies from 17 days to approximately a month after second dose and from 10 days up to a month after third dose. Results from Vassilaki et al showed significant negative correlation between age and IgG titers. (Vassilaki et al., 2021) Antibody levels were found to decline significantly 3 months in comparison to 1 month after the second dose in all age groups, yet still remained significantly lower among the older population (Brockman et al., 2022).

Several studies(Collier et al., 2021; Demaret et al., 2021; Müller et al., 2021) also reported outcomes in terms of neutralizing antibodies. Results were similar to those with anti-spike IgG levels, with majority of studies demonstrating lower titers and proportion of vaccine non-responders in elderly groups (Collier et al., 2021; Demaret et al., 2021; Müller et al., 2021).

Upon third dose vaccination, Mwimanzi et al (Mwimanzi et al., 2022) reported no significant difference in initial antibody responses between older and younger groups, although antibody levels in the elderly vaccinees were shown to be significantly lower after first and second vaccination. There was also no significant difference in neutralizing response between older and younger adults after third dose. (Mwimanzi et al., 2022) Study by Eliakim-Raz et al reported similar result, demonstrating no significant correlation and association between age and IgG titers, but only participants 60 years or older were included in this study (Eliakim-Raz et al., 2021).

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Table 2. Characteristics of selected studies

Author, Year	Location	Sample size	Mean/median age	Type of vaccine	Number of doses	Timing of Ab measurement	Measurement
Müller et al, 2021(Müller et al., 2021)	Germany	176 • <60 years: 93 • >80 years: 83	• <60 years: 42.2 years • >80 years: 87.9 years	BNT162b2	First and second dose	• 17-19 days after 1st dose • 17 days after 2nd dose	anti-S IgG, neutralizing antibodies
Vassilaki et al, 2021(Vassilaki et al., 2021)	Greek	1643	Median 49 years (IQR 40-56)	BNT162b2	First and second dose	• 20-30 days after 2nd dose	anti-RBD IgG
Ramasamy et al, 2020(Ramasamy et al., 2020)	UK	112 • 18-55 years: 39 • 56-69 years: 26 • ≥70 years: 47	-	ChAdOx1 nCoV-19	First and second dose	• 28 days after 2nd dose	anti-S IgG
Collier et al, 2021(Collier et al., 2021)	UK	140 • <80 years: 80 • ≥80 years: 60	Median 72 years (IQR 44-83)	BNT162b2	First and second dose	• 3-12 weeks after 1st dose • 3 weeks after 2nd dose	Serum neutralization
Eliakim-Raz et al, 2021(Eliakim-Raz et al., 2021)	Israel	97 Subject: 60 years or older	Median 70 years (IQR 67-74)	BNT162b2	Third dose	• Before and 10-19 days after third dose	anti-S IgG
Demaret et al, 2021(Demaret et al., 2021)	France	234 • 129 young adults	• Young: median 44 (IQR 39.5-50.5)	BNT162b2	First and second dose	• Day 0 • Day 90 after 1st	anti-S IgG, neutralizing antibodies

		• 105 older residents	• Older: median 86.5 (IQR 81.0-90.0)			dose (±14 days after 2nd dose)	
Brockman et al, 2022(Brockman et al., 2022)	Canada	151 • 89 health care workers • 62 older adults	• HCW: median 41 (IQR 35–50) • Older: median 79 (IQR 73–86)	BNT162b2 or mRNA-1273	First and second dose	• 1 month after 1st dose • 1 month after 2nd dose • 3 months after 2nd dose	anti-RBD IgG
Richards et al, 2021(Richards et al., 2021)	USA	167	Median 42 (IQR 32-57) years	BNT162b2 or mRNA-1273	Second dose	• 7 to 31 days after the 2nd dose	anti-RBD IgG
Mwimanzi et al, 2022(Mwimanzi et al., 2022)	Canada	151 COVID-19 naive • 81 health care workers (HCW) • 56 older adults COVID-19 convalescent • 14 individuals	• HCW: median 41 (IQR 35–51) • Older: median 78 (IQR 73–83) • Convalescent: median 48 (IQR 36–87)	BNT162b2 or mRNA-1273	Third dose	• 1 month after the 3rd dose	anti-S IgG, virus neutralization

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Table 3. Outcomes of Studies

Author, Year	Vaccine	Results
Müller et al, 2021	BNT162b2	Anti-spike IgG: • Anti-spike IgG titers were significantly lower in elderly vaccinees (>80 years) than the younger group (<60 years) after both the first (41.2 BAU/mL vs 313.1 BAU/mL, p<0.0001) and second dose (1332.0 BAU/mL vs 3702.0 BAU/mL, p<0.0001). Neutralizing antibodies • After second dose, 31.3% of the elderly vaccinees had no detectable neutralizing antibodies, in contrast to 2.2% of the younger group
Vassilaki et al, 2021	BNT162b2	Anti-spike RBD IgG: • Significant difference in median of antibody titers across age groups (p<0.0001), with higher titers in younger age groups. • Significant negative correlation between age and IgG titers ($r = -0.2380$, $p = 1.98 \times 10^{-17}$)
Ramasamy et al, 2020	ChAdOx1 nCov-19	Anti-spike IgG: • Titers were similar across three age groups (18-55 years: 20713 AU/mL; 56-69 years: 16170 AU/mL; ≥70 years: 17561 AU/mL; p=0.68)
Collier et al, 2021	BNT162b2	Neutralizing antibodies: • GMT significantly lower in ≥80 years than in <80 years after first dose (48.2 vs 104.1, p=0.004) and second dose (987.2 vs 4894.4, p=0.003).
Eliakim-Raz et al, 2021	BNT162b2	Anti-spike IgG: • No significant correlation between age and IgG titers after third dose (r = -0.075, p=0.47) • Age was not significantly associated with IgG titers (p=0.98)
Demaret et, 2021	BNT162b2	Anti-spike IgG: • Median anti-S IgG titers were 2 times lower among older participants (p<0.001) Neutralizing antibodies: • Neutralizing antibodies were 10 times lower in older than younger participants (p <0.0001) • Number of responders were significantly lower among older than younger participants (p <0.0001)
Brockman et al, 2022	BNT162b2 or mRNA-1273	Anti-spike RBD IgG: • After first dose: median IgG 2.5-fold lower in COVID-19-naïve older adults compare to younger groups (p <0.0001) • After second dose: median IgG remained 2-fold lower among older adults (p <0.0001) • Three months after second dose: response declined significantly in all participants and is still significantly lower in the older adults • Multivariate analysis: older age was significantly negatively associated with IgG responses 1 month after first (p =0.0001) and second dose (p =0.0002)

Richards et al, 2021	BNT162b2 or mRNA-1273	BNT162b2: • After second dose, participants ≥50 years old had lower IgG levels than younger groups (31.1 µg/mL [95% CI, 19.9-48.7] vs 59.0 µg/mL [95% CI, 48.8-71.4]) mRNA-1273: • No significant difference in antibody levels after second dose between older and younger adults.
Mwimanzi et al, 2022	BNT162b2 or mRNA-1273	Anti-spike IgG: • Antibody levels in older adults were significantly lower than younger adults 1 month after first ($p < 0.0001$) dose and 1, 3, and 6 months after second ($p < 0.0001$) dose • No significant difference in antibody response between older and younger adults 1 month after third dose ($p=0.33$) Neutralization: • No significant difference in neutralizing response between older and younger adults after third dose ($p=0.6$)

Discussion

This systematic review highlights the lower immunogenicity in response to COVID-19 vaccination in older adults. This is especially important as COVID-19 has been known to take an especially devastating toll on the elderly population. (Gold et al., 2020) Overall, majority of studies included in this review displayed lower immune responses toward first and second doses of COVID-19 vaccine among the elderly; however, responses were comparable across age groups after administration of third dose. Immunogenicity was also found to be similar between different age groups in mRNA-1273 and ChAdOx1 vaccines, but the paucity of studies evaluating responses in the elderly for vaccines other than BNT162b2 poses a challenge in concluding their immunogenicity with the current evidence.

Effective vaccine response involves the activation of effector cells and memory cell formation. This is primarily manifested by the presence of adequate antibody concentration to neutralize the pathogen as well as a sufficient recall response when the similar pathogen is encountered in later life. (Gustafson et al., 2020) Older population, however, often presents with both defective early and recall responses, as demonstrated by lower antibody response after first and second doses of vaccine. This is additionally supported by the findings of lower neutralization potential in the elderly, in which neutralization level is found to be highly predictive for protection against SARS-CoV-2 infection (Khoury et al., 2021)

The difference in the responses across age groups may be explained by the previous theory of immunosenescence in the elderly. Immunosenescence is defined as the alteration in immune system associated with ageing. Low-grade, persistent chronic inflammation is found to be increased in association with aging, and this is hypothesized to drive many age-related chronic diseases as well as a contributor to immunosenescence. The presence of constantly elevated proinflammatory cytokines result in high basal activation, but suboptimal immune response in face of acute challenges. (Bartleson et al., 2021) This constant low-grade inflammation is commonly known as ‘inflammaging’, which is responsible of creating an environment detrimental to adequate vaccine response generation. (Fulop et al., 2022) Furthermore, the dysregulation in immune system also results in a defective generation of robust adaptive immune system, diminishing protective response to infection and vaccination among older vaccinees. (Pawelec & Weng, 2020) Following recognition of vaccine antigens by innate immune system, adequate priming of adaptive immune response and memory cells formation is a key process in developing vaccine immunogenicity. However,

several alterations in the adaptive arm of older individuals are found to contribute to altered vaccine response. Collectively, these include decrease in number of naïve CD8+ T cells prior to vaccination, lower T cells activation, as well as lower effector response and neutralizing capacity of antibodies generated from T cells of older adults. (Connors et al., 2021) Age was still found to be significantly associated with poorer antibody response even after controlling for a number of chronic conditions which may exacerbate immune system dysregulation in the elderly, thus remaining as an independent predictor of diminished response to vaccination (Brockman et al., 2022).

Study by Mwimanzi et al emphasized the benefit of third dose administration in the older population. It was found that younger and older groups mounted comparable antibody levels and neutralizing capability a month after the third dose. (Mwimanzi et al., 2022) Similary, a previous study has shown that repeated vaccination for influenza A infection resulted in improved memory B cell response. (Frasca et al., 2016) These findings support the fact that repeated events of immune stimulation are needed in older adults to achieve antibody levels comparable to younger individuals. (Luczkowiak et al., 2023) Various strategies have been implemented to overcome the problem of diminished vaccine response in older adults, including increasing the vaccine dose, utilization of adjuvants and using alternative administration route. (Schenkelberg, 2021) Providing a booster dose, therefore, may be a strategy to improve COVID-19 vaccine response among the elderly. However, only early antibody response to the third dose was assessed in this study. Considering a significant decline in antibodies over time after the second dose (Brockman et al., 2022), the durability of response upon third dose administration warrants further investigation.

The results of this systematic review show that first and second dose of COVID-19 vaccines elicited suboptimal immune response in older population; notably, a third dose administration is important in achieving post-vaccination antibody levels comparable to that of younger groups. Given the ongoing transmission of COVID-19 in present times, these results highlight the benefit of a booster dose particularly in older adults. Furthermore, these findings may help to encourage public health decision-makers to prioritize booster doses to the elderly particularly in settings of limited resources, such as in developing countries, where booster COVID-19 vaccines may not be readily available for all population.

This systematic review also presents with several limitations. Almost all of the studies included in the review investigated responses of mRNA vaccines, thus the effect of other types of vaccine on the older population remains largely unexplored. Moreover, the assessment on the durability of vaccine response was still lacking; further studies with longer follow-up duration after vaccine administration may be required in order to determine the optimal booster interval, particularly among the elderly.

Conclusion

In conclusion, this systematic review highlights decreased immunogenicity towards COVID-19 vaccines in older population. Further research into strategies to improve vaccine responses in the elderly is required to protect this vulnerable group.

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