The Efficacy of SARS-CoV-2 Vaccination in the Elderly: A Systemic Review and Meta-analysis

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ABSTRACT

BACKGROUND: Given the reduced immune response to vaccines in older populations, this study aimed to evaluate the efficacy of COVID-19 vaccinations and its impact on breakthrough infection, hospital admission, and mortality in the elderly.

METHODS: We carried out a systemic review and meta-analysis where MEDLINE, Web of Science, EMBASE, ClinicalTrials.gov, and Cochrane Central Register for Controlled Trials were queried to identify relevant literature. We included randomized controlled trials (RCTs), non-randomized trials, prospective, observational cohort, and case–control studies assessing breakthrough infection, hospital admission, and mortality after coronavirus 2 (SARS-CoV-2) vaccination in the elderly (≥ 60 years old).

RESULTS: Overall, 26 studies were included in this meta-analysis. Compared with the unvaccinated group, the vaccinated group showed a decreased risk of SARS-CoV-2 infection after 28–34 (relative risk [RR] = 0.42, 95% confidence interval [CI] 0.37–0.49) and 35–60 days (RR = 0.49, 95% CI 0.37–0.62). There was a step-wise increase in efficacy with additional doses with the two-dose group experiencing decreased risk of breakthrough infection (RR = 0.37, 95% CI 0.32–0.42), hospital admissions (RR = 0.25, 95% CI 0.14–0.45), disease severity (RR = 0.38, 95% CI 0.20–0.70), and mortality (RR = 0.21, 95% CI 0.14–0.32) compared with those receiving one or no doses. Similarly three-dose and four-dose vaccine groups also showed a decreased risk of breakthrough infection (3-dose: RR = 0.14, 95% CI 0.10–0.20; 4-dose RR = 0.46, 95% CI 0.4–0.53), hospital admissions (3-dose: RR = 0.11, 95% CI 0.07–0.17; 4-dose: RR = 0.42, 95% CI 0.32–0.55), and all-cause mortality (3-dose: RR = 0.10, 95% CI 0.02–0.48; 4-dose: RR = 0.48, 95% CI 0.28–0.84) Subgroup analysis found that protection against mortality for vaccinated vs. unvaccinated groups was similar by age (60–79 years: RR = 0.59; 95% CI, 0.47–0.74; ≥ 80 years: RR = 0.76; 95% CI, 0.59–0.98) and gender (female: RR = 0.66; 95% CI, 0.50–0.87, male: (RR = 0.58; 95% CI, 0.44–0.76), and comorbid cardiovascular disease (CVD) (RR = 0.69; 95% CI, 0.52–0.92) or diabetes (DM) (RR = 0.59; 95% CI, 0.39–0.89.

CONCLUSIONS: Our pooled results showed that SARS-CoV-2 vaccines administered to the elderly is effective in preventing prevent breakthrough infection, hospitalization, severity, and death. What's more, increasing number of vaccine doses is becoming increasingly effective.

Yang XH, Bao WJ and Zhang H contributed equally to this paper.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections have posed a serious threat to global human health over the past three years. Preventive strategies for SARS-CoV-2 transmission and infection include effective isolation, the use of vaccinations and the use of antiviral drugs. Specific mRNA, viral-vector-based, and inactivated SARS-CoV-2 vaccines are being used worldwide. While efficacy of vaccines have been confirmed in adults [1–3], there is a debate regarding the outcomes of vaccination in the elderly [4,5]. Several factors affect vaccine efficacy including age, prior antigen exposure, vaccine schedule, and vaccine dose [6]. Older populations tend to have poorer immune responses to vaccines with a decline in immune function with age[7]. In some countries older adults have lower vaccination rates and higher vaccine hesitancy than younger adults [8–10]. Comorbidities, vaccine hesitancy, or lower vaccination rates, are important causes for increased infection and death in the elderly. Moreover, the size and proportion of the elderly population has been increasing worldwide.

Our study purpose was to assess the effectiveness of the SARS-CoV-2 vaccine to reduce the risks of breakthrough SARS-CoV-2 infection, virial-associated hospital admission, and mortality among adults greater than 60 years of age.

METHODS

We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This study is registered with PROSPERO (number CRD42022372066).

Search strategy and study selection

We queried MEDLINE (PubMed, January 1, 2020, to December 31, 2022), Web of Science, EMBASE (January 1, 2020, to December 31, 2022), ClinicalTrials.gov, and

Cochrane Central Register of Controlled Trials. The search strategy was shown in the Supplemental Table 1. Manual searches of references cited by the identified original studies and relevant review articles were also performed, and the selected papers were evaluated. We did not use a reference librarian in creating or conducting these searchers.

Inclusion and exclusion criteria

Studies that met the following criteria were included in our meta-analysis: 1) Age ≥ 60 years old; 2) randomized controlled trials (RCTs), non-randomized trials, and observational studies; 3) vaccinated groups compared with unvaccinated groups; and 4) availability of an outcome (breakthrough infection, hospital admissions, severity of disease, or all-cause mortality).

Studies were excluded if they met any of the following criteria: 1) the study was not in English; 2) different publications analyzing the same population or duplicates.

We defined a breakthrough infection as a SARS-CoV-2 infection confirmed by positive laboratory nucleic acid after 14 days of any SARS-CoV-2 vaccination.[11]

Data collection

Three researchers performed the searches and reviewed the results. Data were independently extracted by all three researchers. From each study, we extracted data on author, year, country, study design, sample size, age, sex, vaccine type, homologous or heterologous vaccinations, prior SARS-CoV-2 infection, vaccine dose, follow-up, virus type and outcomes. The primary outcome was the occurrence of breakthrough SARS-CoV-2 infection. Secondary outcomes included hospital admissions, disease severity, and all-cause mortality. We defined a severe disease as respiratory failure requiring mechanical ventilation or shock or other organ failures requiring Intensive Care Unit (ICU) care.

Relative risks (RRs) (and 95% CI) were either calculated or extracted from individual studies. Any disagreement in data extraction was resolved through discussion among the researchers in consultation with other authors and a consensus was reached.

Risk of bias assessment

The risk of bias in non-randomized studies of interventions (ROBINS-I) tool was also used to assess the quality of the included non-RCTs. Studies were ranked as low, moderate, serious, or critical risk of bias in the seven domains (confounding, selection of participants in to the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result). Low risk: the study is evaluated to be at low risk of bias for all domains. Moderate risk: the study is evaluated to be at low or moderate risk of bias for all domains. Serious risk: the study is evaluated to be at serious risk of bias in at least one domain, but not at critical risk of bias in any domain. Critical risk: the study is evaluated to be at critical risk of bias in at least one domain. Any discrepancies were resolved through discussion with a third author (Jin HM) and consensus was reached.

Statistical analyses

Data were analyzed using a random effects model (STATA,version 14.0; StataCorp LLC, TX, USA, metan command). According to the follow-up time (14–20 days, 28–34 days and 35–60 days), we used subgroup analyses to evaluate breakthrough infection comparisons of different levels of vaccination (none, one, two, three or four doses). Heterogeneity was assessed with the I^2 statistic, while subgroup analysis and meta-regression (restricted maximum likelihood (REML) heterogeneity estimator) were performed to identify sources of heterogeneity. Sensitivity analyses were done to evaluate the effects of age, gender and different disease conditions on the risk of hospital admissions, the severity of disease, or mortality. We also assessed whether any study was overly influential by stepwise elimination. The Egger's test was used to investigate the presence of publication bias. If there was any publication bias, it was adjusted using the trim-and-fill method with the "meta trim" command. Statistical significance for all analyses was set at $P < 0.05$.

RESULTS

Study flow and characteristics

The PRISMA chart is presented in Figure S1. Overall, 26 studies were included in this meta-analysis [11–36]. Overall, there were 26 studies involving 8,968,085 participants that were included (Table 1). Sample sizes ranged from 98 to 2,413,356 participants with age ≥ 60 years old and the proportions of men in study populations ranged from 30 to 95%. Of the 26 included studies, 21 studies were prospective or retrospective cohort studies, 5 case–control studies and no randomized controlled trials (RCTs). Included studies came from the US, UK, Qatar, Israel, Spain, Italy, Pakistan, France, Denmark, China, Portugal, Hungary, and Sweden.

Relative risks for breakthrough SARS-CoV-2 infection, hospital admissions, and all-cause mortality after one dose of vaccine in the elderly. Compared to unvaccinated elders, one dose did not reduce risk of breakthrough SARS-CoV-2 infection in the first 14–20 days (RR = 0.81, 95% CI 0.63–1.05, I^2 = 87%, n = 2 studies). However, by 28–34 days (RR = 0.42, 95% CI 0.37–0.49, I^2 = 0%, n = 3 studies) and 35–60 days (RR = 0.49, 95% CI: 0.37–0.62, I^2 = 47%, n = 4 studies), one dose decreased risk of breakthrough SARS-CoV-2 infection (Fig. 1A).

One dose also reduced the risk of hospital admissions (RR = 0.43, 95% CI 0.37–0.51, I^2 = 72%, n = 4 studies; (Fig. 1B)) and all-cause mortality (RR = 0.59, 95% CI 0.47–0.74, I^2 = 68%, n = 3 studies; (Fig. 1B)).

Table 1 Characteristics of 26 studies

Study	Country	Study design	Sample size	Age (years)	Men, %	Vaccine type	homologous or heterologous vaccinations	Prior SARS-CoV-2 infection	Dose	follow-up	Virus type	outcomes
Lopez Bernal J et al. [11]	UK	case–control study	44,590	≥ 60	NA	BNT162b2 or ChAdOx1	homologous	mixed	2	≥ 35 days	B.1.1.7	Breakthrough infection Hospitalization All-cause mortality
Butt AA et al. [12]	Qatar	retrospective cohort study	98	≥ 60	60.7	BNT162b2 or mRNA-1273	homologous	No	2	3 months	NA	Hospitalization Severity of disease
Butt AA et al. [13]	Qatar	retrospective cohort study	171	≥ 60	95.31	BNT162b2	homologous	No	2	3.5 months	NA	Hospitalization Severity of disease
Haas EJ et al. [14]	Israel	retrospective cohort study	1,127,965	≥ 65	72.2	BNT162b2	homologous	No	2	69 days	B.1.1.7	Hospitalization
Hyams C et al. [15]	UK	case–control study	466	≥ 80	50	BNT162b2 or ChAdOx1	/	No	1	60 days	B.1.1.7	Breakthrough infection
Martínez-Baz I et al. [16]	Spain	prospective cohort study	4539	≥ 60	49.1	BNT162b2 or ChAdOx1	homologous	No	2	3 months	B.1.1.7	Breakthrough infection
Naleway AL et al. [17]	US	retrospective cohort study	90,971	≥ 65	55.6	BNT162b2 or ChAdOx1	homologous	No	2	≥ 14 days	Delta	Breakthrough infection Hospitalization
Rivasi G et al. [18]	Italy	retrospective cohort study	3730	84	31	BNT162b2	homologous	mixed	2	6 months	NA	Breakthrough infection Hospitalization Severity of disease
Shrotri M et al. [19]	UK	prospective cohort study	10,412	≥ 80	30.4	BNT162b2 or ChAdOx1	/	No	1	49 days	B.1.1.7	Breakthrough infection
Tenforde MW et al. [20]	US	retrospective cohort study	417	≥ 65	52	BNT162b2 or mRNA-1273	homologous	No	2	3 months	NA	Hospitalization
Vasileiou E et al. [21]	UK	prospective cohort study	861,033	≥ 65	40	BNT162b2 or ChAdOx1	/	No	1	42 days	NA	Hospitalization
Aslam J et al. [22]	Pakistan	prospective cohort study	85	≥ 66	57.7	mRNA-1273 or BNT162b2 or ChAdOx1	/	No	1	4 months	NA	All-cause mortality
Bar-On YM et al. [23]	Israel	retrospective cohort study	1,252,331	≥ 60	48.2	BNT162b2	homologous	No	4	56 days	omicron	Hospitalization Severity of disease
Suarez Castillo M et al. [24]	France	case–control study	2,413,356	≥ 60	48	mRNA-1273 or BNT162b2 or ChAdOx1	homologous	No	2	≥ 14 days	omicron	Breakthrough infection
Gazit S et al. [25]	Israel	case–control study	97,499	≥ 60	45.7	BNT162b2	homologous	mixed	4	2 months	omicron	Breakthrough infection Hospitalization Severity of disease All-cause mortality
Goldin S et al. [26]	US	Nationwide Cohort study	43,596	≥ 65	NA	BNT162b2	homologous	No	2	28 days	NA	Breakthrough infection All-cause mortality
Gram MA et al. [27]	Denmark	Nationwide Cohort study	30,237	≥ 60	46.7	BNT162b2 or mRNA-1273	homologous	No	3	3 months	alpha/delta/omicron	Breakthrough infection
Kelly JD et al. [28]	US	retrospective nationwide Cohort study	1,100,280	≥ 65	91.8	BNT162b2 or mRNA-1273	heterologous	No	3	5 months	delta/omicron	Hospitalization All-cause mortality

Table 1 (continued)

Study	Country	Study design	Sample size	Age (years)	Men, %	Vaccine type	homologous or heterologous vaccinations	Prior SARS-CoV-2 infection	Dose	follow-up	Virus type	outcomes
Lu G et al. [29]	China	retrospective cohort study	1377	≥ 60	46.62	inactived	homologous	No	2	1 months	omicron	Hospitalization Severity of disease
Machado A et al. [30]	Portugal	retrospective cohort study	1,884,932	≥ 65	44.6	mRNA-1273	homologous	No	2	98 days	NA	Breakthrough infection Hospitalization All-cause mortality
Magen O et al. [31]	Israel	retrospective cohort study	258,994	≥ 60	49	BNT162b2	homologous	No	4	46 days	omicron	Breakthrough infection Hospitalization Severity of disease All-cause mortality
Muhsen K et al. [32]	Israel	retrospective cohort study	18,611	≥ 60	31.7	BNT162b2	homologous	No	3	63 days	NA	Breakthrough infection Hospitalization All-cause mortality
Muhsen K et al. [33]	Israel	prospective cohort study	43,775	≥ 60	32.2	BNT162b2	homologous	No	4	73 days	omicron	Breakthrough infection Hospitalization Severity of disease All-cause mortality
Müller V et al. [34]	Hungary	nationwide, retrospective cohort study	1,984,176	≥ 65	38.8	mRNA-1273 or BNT162b2 or ChAdOx1	heterologous	mixed	3	3.25 months	delta	Breakthrough infection Hospitalization All-cause mortality
Nordström P et al. [35]	Sweden	nationwide, retrospective cohort study	24,524	≥ 80	32.2	BNT162b2 or mRNA-1273	heterologous	No	4	2 months	omicron	All-cause mortality
Tenforde MW et al. [36]	US	test-negtive case–control study	1653	≥ 65	56.1	BNT162b2 or mRNA-1273	homologous	No	2	28 days	alpha/delta	Hospitalization

Homologous vaccinations, the same immunogen vaccination regimen; Heterologous vaccinations, the different immunogen vaccination regimen

Relative risks for breakthrough SARS-CoV-2 infection, hospital admissions, the severity of disease and all-cause mortality after two doses of vaccine in the elderly. Those receiving two doses had decreased breakthrough infections compared with the one or no doses (RR = 0.37, 95% CI 0.32–0.42, I^2 = 59%, n = 9 studies; (Fig. 2)). Compared to the first-dose vaccine or unvaccinated group, the two-dose vaccine group also decreased hospital admissions (RR = 0.25, 95% CI 0.14–0.45, I^2 = 86%, n = 10 studies; (Fig. 2)), disease severity (RR = 0.38, 95% CI 0.20–0.70, I^2 = 47%, n = 4 studies; (Fig. 2) and mortality(RR = 0.21, 95% CI 0.14–0.32, I^2 = 53%, n = 3 studies; (Fig. 2).

Relative risks of breakthrough SARS-CoV-2 infection, hospital admissions, and all-cause mortality after three doses of the vaccine in the elderly. Similarly, the three-

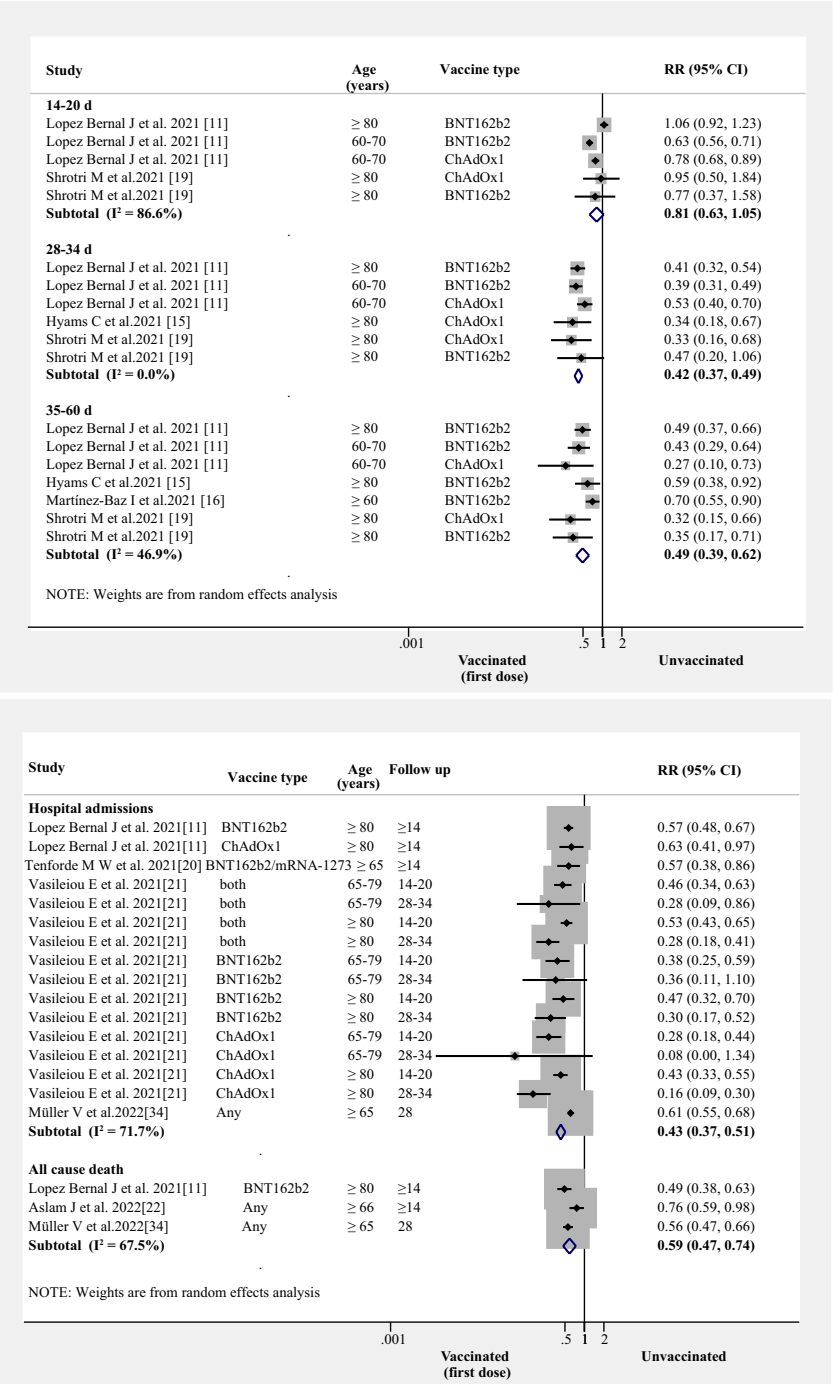

Figure 1 RRs for breakthrough SARS-CoV-2 infection, hospital admissions, and all-cause mortality after the first dose of vaccine (A) RRs for breakthrough SARS-CoV-2 infection associated with the first dose of vaccine (B) RRs for hospital admissions and all-cause mortality associated with first dose of vaccine. (Both: BNT162b2 and mRNA-1273; Any: BNT162b2 or ChAdOx1 or mRNA-1273, et al.)

dose vaccine group showed a decreased risk of breakthrough infection (RR = 0.14, 95% CI 0.10–0.20, I^2 = 82%, n = 3 studies), hospital admissions (RR = 0.11, 95% CI 0.07–0.17, I^2 = 76%, n = 4 studies), and all-cause mortality (RR = 0.10, 95% CI 0.02–0.48, I^2 = 74%, n = 3 studies) compared to the two-dose vaccine or less group in the elderly (Fig. 3).

Relative risks for breakthrough SARS-CoV-2 infection, hospital admissions, the severity of disease, and all-cause mortality after four vaccine doses in the elderly. The four-dose vaccine group was associated with decreased breakthrough infections when compared with the three-dose vaccine group (RR = 0.46, 95% CI 0.40–0.53, I^2 = 78%, n = 4 studies; (Fig. 4)). Compared with the three-dose vaccine group, the four-dose vaccine group also showed a decreased risk of hospital admissions (RR = 0.42, 95% CI 0.32–0.55, I^2 = 87%, n = 4 studies; (Fig. 4)) and disease severity (RR = 0.44, 95% CI 0.35–0.57, I^2 = 83%, n = 4 studies; (Fig. 4)). Similarly, pooled results from four studies indicated that a four-dose vaccine was associated with a decreased risk of mortality compared with the three-dose or fewer vaccine group (RR = 0.48, 95% CI 0.28–0.84, I^2 = 88%, n = 4 studies; (Fig. 4)).

Subgroup and meta-regression analysis of relative risks for hospital admissions, the severity of disease and all-cause mortality. Age, sex, comorbid conditions, and vaccination type were potential confounders related to hospital admission, disease severity and all-cause mortality. As shown in Figure S2, the estimated RR indicated that age groups 60–74 years and ≥ 75 years experienced a decreased risk of hospital admissions in the vaccinated group (RR = 0.42, 95% CI 0.33–0.53; RR = 0.33, 95% CI 0.16–0.65, respectively) compared to the unvaccinated group. Similarly, the estimated RR indicated that age groups 60–69 years and 70–79 years were also associated with a decreased risk of the severity of disease (RR = 0.45, 95% CI 0.30–0.68; RR = 0.53, 95% CI 0.36–0.79, respectively; Figure S3). Furthermore, in the vaccinated groups, it was found that age groups 60–79 years (RR = 0.59; 95% CI, 0.47–0.74), age groups ≥ 80 years (RR = 0.76; 95% CI, 0.59–0.98), female (RR = 0.66; 95% CI, 0.50–0.87), male (RR = 0.58; 95% CI, 0.44–0.76), and coexistence with CVD (RR = 0.69; 95% CI, 0.52–0.92) and DM (RR = 0.59; 95% CI, 0.39–0.89) showed a significantly lower risk of all-cause mortality in comparison with the unvaccinated group (Figure S4). The meta-regression demonstrated that sample size and comorbid conditions influenced the hospital admissions, vaccine dose and comorbid conditions influenced the severity of disease, and study design and comorbid conditions influenced all-cause mortality. The summary of the meta-regression of the hospital admissions, the severity of disease and all-cause mortality among vaccinated groups can be found in the Supplemental Table 2.

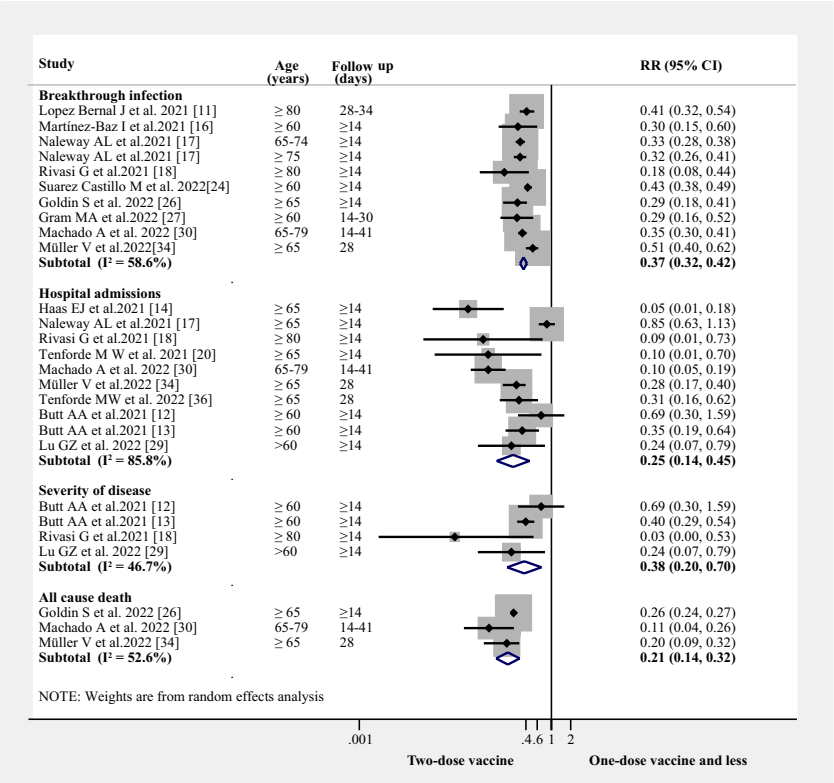

Figure 2 RRs for breakthrough SARS-CoV-2 infection, hospital admissions, the severity of disease, and all-cause mortality after two-dose of the vaccine

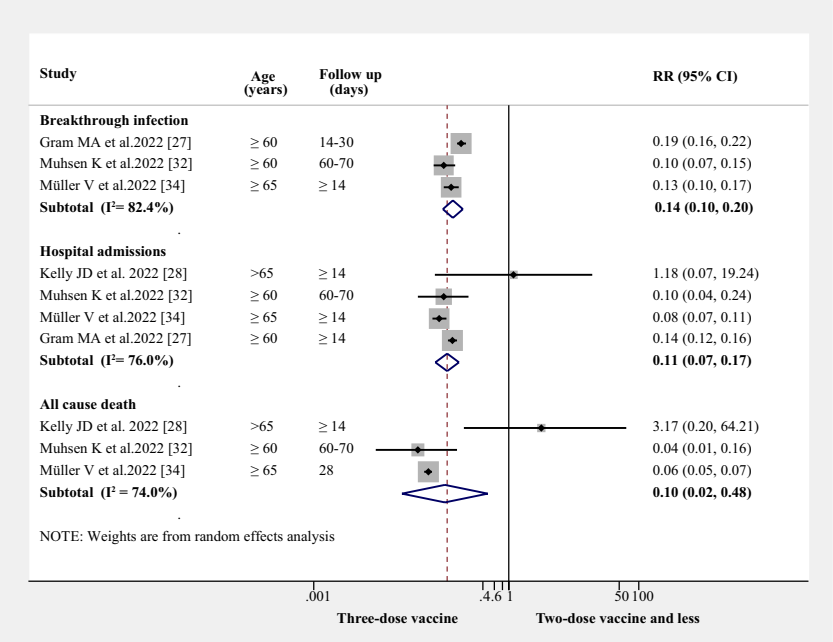

Figure 3 RRs for breakthrough SARS-CoV-2 infection, hospital admissions, and all-cause mortality after three-dose of the vaccine

Comparison of efficiency of homologous and heterologous vaccination. All two dose studies were homologous vaccinations. Only three trials reported on heterologous vaccination after three or four doses of vaccination. Both of the homologous and heterologous vaccination had similar effects in the prevention of hospital admission and mortality due to SARS-CoV-2 infection (Figure S5).

Sensitivity analysis and publication bias

No study was overly influential, excluding any single study did not change our results. We also found no evidence of publication bias was found in the pooled studies on breakthrough infection, breakthrough infection ($p = 0.17$), disease severity ($p = 0.77$) or all-cause mortality ($p = 0.53$).

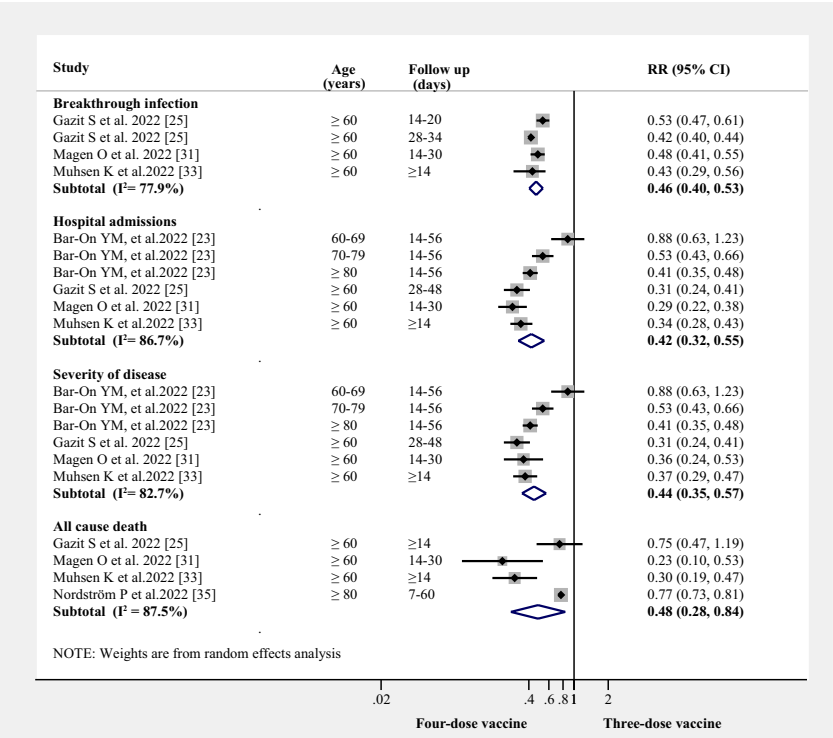

Figure 4 RRs for breakthrough SARS-CoV-2 infection, hospital admissions, the severity of disease, and all-cause mortality after four-dose of the vaccine

However, there was a significant publication bias in hospital admissions ($P=0.03$). After adjustment for potentially missing studies, hospital admissions was reduced among those who were vaccinated (RR: 0.346, 95% CI 0.285–0.420).

Risk of bias assessment. The detailed risk assessment for the included studies using the ROBINS-I tool is shown in the Supplemental Table 3. Eight studies were assessed as low risk of overall bias; 18 studies were graded as of moderate risk of overall bias. No studies were assessed to have severe or critical bias.

DISCUSSION

Our meta-analysis of 26 trials showed that the SARS-CoV-2 vaccine is effective in preventing SARS-CoV-2 breakthrough infections, hospital admissions, and mortality in the elderly, regardless of whether they receive one, two, three, or four doses. We also found that each additional dose of vaccine increased the benefit.

Increasing age is the most significant risk factor for SARS-CoV-2-related death among the non-vaccinated population [37]. Several studies have reported weaker vaccine-induced immune responses in older adults, including lower concentrations of neutralizing antibodies, than in younger adults [38,39]. While immunological studies suggest that these vaccinations would be less effective in the elderly, our pooled results support vaccine effectiveness against SARS-CoV-2, with increasing effectiveness with additional doses.

There are concerns whether excessive injection of vaccine boosters may lead to damage to the body's immune system and a low immune response. Studies in mice suggest that there is a reduction of the overall immune responses in both the titer of RBD-specific antibodies and the serum neutralizing potency against SARS-CoV-2 pseudo-viruses, with three boosters, indicating that repetitive administration of RBD vaccine boosters might induce humoral immune tolerance, rather than promote immunity [40,41]. Our study suggests that four doses of vaccination leads to improved protection. At present, the optimum number of vaccination boosters is uncertain, but the potential immune suppression by continuous use of SARS-CoV-2 vaccine boosters should raise concern and studies are needed to confirm whether this occurs in humans, especially in the older population due to age-related changes of the immune system.

There are several limitations to this meta-analysis. First, our results are based on relatively few trials for each outcome. Secondly, some of our analyses had high levels of heterogeneity. This may be due to different age stratification and variable follow-up intervals in several of the included studies. Third, this meta-analysis only studied the main outcomes at 14–20 days, 28–34 days, and 35–60 days. Studies on long-term vaccine protection are lacking, and future studies are needed to further investigate whether more boosters are needed in vulnerable older people and the timing of such boosters. Fourth, we cannot assess the side effects of the vaccines, because trials did not describe vaccine side effects. Future research should report side effects of vaccines in the elderly.

In summary, we found that SARS-CoV-2 vaccine is effective in preventing breakthrough infections, infection severity, hospitalization and mortality. Increasing number of boosters was associated with greater benefit.

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Authors' contributions *HM Jin and SK Fu conceived and designed the study. XH Yang, H Zhang and WJ Bao selected the articles, extracted, and analyzed the data. XH Yang, H Zhang and WJ Bao wrote the first draft of the manuscript. XH Yang and WJ Bao interpreted the data and contributed to the writing of the final version of the manuscript. All authors agreed with the results and conclusions of this Article.*

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Data Availability *The data used of this meta-analysis are available from the corresponding author.*

Declarations

Conflicts of interest *None of the authors had any conflicts of interest.*

Competing interests *The authors declare that they have no competing interests.*

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