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The immunogenicity of an inactivated vaccine against SARS-CoV-2 in healthy individuals: A systematic review and meta-analysis

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ABSTRACT

Objective: Inactivated (killed) vaccines against COVID-19 have been widely used for the control of the pandemic condition. We performed a systematic and meta-analysis review of randomized, double-blind, placebo-controlled trials of the immunogenicity of inactivated vaccines against SARS-CoV-2 in healthy individuals.

Methods: In the present study, all research and evidence were extracted from the available online databases. Two researchers randomly evaluated the assessment of the research sensitivity. Finally, after quality assessment and regarding the specific inclusion and exclusion criteria, the eligible articles were entered for meta-analysis. The heterogeneity between the results of the studies was measured using test statistics (Cochran’s Q) and the I² index. The forest plots illustrated the point and pooled estimates with 95% confidence intervals (crossed lines). All statistical analyses were performed using Comprehensive meta-Analysis V.2 software.

Results: This meta-analysis included six primary studies investigating the immunogenicity of inactivated vaccines against SARS-CoV-2 in healthy individuals. According to the pooled prevalence (95% confidence interval), neutralizing antibody responses 28 days after receiving the second dose regarding different ages and micrograms per dose was 95.50% (CI: 93.2–97.1%). Our results showed that antibody levels were higher in the 6 μg group than in other groups. 98.3% (CI: 94.2–99.5%).

Conclusion: Since the rapid development of vaccinations has sparked widespread public anxiety regarding vaccine efficacy. Governments and unvaccinated individuals, particularly those with vaccination reluctance, will be interested in and benefit from the findings of this systematic study.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative of coronavirus disease 2019 (COVID-19), poses a foremost challenge to public health. Since the primary appearance of SARS-CoV-2 in late December 2019 in Wuhan, Hubei province, central China, a high dissemination rate has been observed worldwide [1]. Based on information released by the World Health Organization (WHO) on 29 December 2020, the present pandemic COVID-19 has recorded almost 260 million confirmed cases and 5.2 million deaths worldwide [2]. Compared to other coronaviruses, SARS-CoV-2 benefits from more transmission power [3,4]. It seems that vaccination programs play a critical role in the prevention and control of COVID-19. Although social distancing and local quarantine programs are effective in reducing the incidence of COVID-19 in a short time, a lack of adequate herd immunity can prolong the duration of SARS-CoV-2 outbreaks [5]. Various vaccine platforms including DNA and RNA vaccines, inactivated vaccines, protein subunit vaccines, and virus-like particle vaccines are under evaluation in clinical trials. Most COVID-19 vaccines elicit robust antibody response against spike antigen of SARS-CoV-2 [6] that are highly protective [7]. Among the mentioned platforms, inactivated (killed) vaccines have been widely used for prophylaxis against the disease [8]. This group of COVID-19 vaccines triggers innate and adaptive immunity through a variety of mechanisms that lead to the production of specific antibodies which bind the spike protein and prohibit the virus entry into the host cells [9,10]. Serological tests have been developed for the detection of antibodies against SARS-CoV-2’s nucleocapsid (N) and spike (S) antigens [11]. In fact, measuring antibody response could help...
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Fig. 1. Flow chart of the literature search strategy for selection and including primary articles.

drawing a conclusion on the effectiveness of vaccination strategies. Given that people aged 60 and older are at higher risk of developing a fatal disease compared to the younger individuals, it seems that choosing the effective vaccination program plays a key role in the management of COVID-19. However, there might be a series of public doubts towards the general vaccination programs or against certain categories of vaccines. Accordingly, irresponsible rumors might affect the public adherence to vaccination programs. Thus, the aim of the present study was to establish an un-biased systematic review and meta-analysis of the randomized clinical trials to draw a conclusion on the effectiveness of inactivated vaccines that are among the generally used biologics in some nations for providing prophylaxis against SARS-CoV2.

2. Methods

2.1. Search strategy

In the present study, the search strategy was done using available online national databases, including ISI, Science Direct, Scopus, PubMed, Wiley, and Google scholar between 2020 and 2022. The search was performed based on appropriate keywords of SARS-CoV-2, inactivated vaccines, clinical trial, COVID-19, immunogenicity, safety, placebo-controlled, and double-blind which were combined with and/or/not to determine and screen articles in the search strategy. Besides, it investigated the references of the published studies to improve the sensitivity of the search. The assessment of research was randomly carried out by two researchers and confirmed that all suitable studies had been detected.

2.2. Study selection

At first, articles of all research, evidence, or reports were extracted from the electronic databases. After examinations of the studies, duplicate articles were identified and removed from the study. Then, irrelevant articles were excluded by reviewing the title, abstract, and full texts of the articles. Besides, the literature review articles and articles published in other languages were excluded from the study accordingly.

2.3. Quality assessment

The NOS checklist (NEWCASTLE-OTTAWA QUALITY ASSESSMENT SCALE) was used for the evaluation of the quality of the related studies and the determination of the selected studies based on title and contents. The NOS checklist is consists up of 8 items covering different aspects of representativeness of the cases, case definition, selection of controls, the definition of controls, comparability of cases and controls, and exposure [12].

2.4. Inclusion/exclusion criteria

All articles approved by the above assessment phases were considered eligible for final meta-analysis: 1) All English studies. 2) Clinical trial studies based on the immunogenicity of an inactivated SARS-CoV-2 vaccine. 3) Clinical trial studies were conducted on healthy individuals.
The forest plots illustrated the point and pooled estimates with 95% confidence intervals. 5) Articles with no access to the full text.

2.5. Data extraction

After the selection of appropriate articles, the following data for each research were extracted based on the first author’s name, geographical region, publication year, number of participants, vaccine doses, number of participants who received 8 different doses (1.5, 2, 3, 4, 5, 6, 8, and 10 μg) of vaccine concentration on days 0–14, and 0–28. The data were extracted and entered into a Microsoft Excel spreadsheet.

2.6. Statistical analysis

The primary outcome was the immunogenicity of inactivated vaccines against SARS-CoV-2 in healthy individuals in terms of antibody response. In our research, the heterogeneity between the results of studies was measured using the test statistic (Cochran’s Q) and the I² index. A P-value <0.1 was used to consider significant heterogeneity. The forest plots illustrated the point and pooled estimates with 95% confidence intervals (crossed lines). Each box in a forest plot indicated the study’s weight. The heterogeneity and homogeneity of the suspected factors were performed using random and fixed effects models, respectively, and >50% were considered as high degrees of heterogeneity. All statistical analyses were performed using CMA (Comprehensive Meta-Analysis V.2) software.

3. Results

In the present study, 1380 articles were identified in the retrieval process. The studies were reduced to 900 following the removal of non-relevant articles. In the next step, 480 articles were considered for further screening. After the exclusion of 151 duplicate articles, 329 articles were assessed for eligibility. Then, 323 articles were removed after screening. Finally, 6 relevant articles were included in the Meta-analysis review (Fig. 1). The seroconversion rates of neutralizing antibody responses to SARS-CoV-2 among the participants are shown in Tables 1 and 2 categorized by age and the micrograms per dose of the vaccine 28 days after receiving the second dose. The lowest seroconversion rate was associated with the 1.5 μg dose of vaccine that caused 90.4% seroconversion (CI: 78.7–96.1%). In contrast, the highest seroconversion was experienced in the case of the 6 μg dose which caused a 98.3% seroconversion rate (CI: 94.2–99.5%). The 6 μg-receiving participants showed a trend for a higher seroconversion than the other individuals (98.3%; CI: 94.2–99.5%).

The forest plot analysis showed that neutralizing antibody responses to SARS-CoV-2 among the participant 28 days after the second dose by age and micrograms per dose.

Table 1

| Ref | Author | Area | clinical trial phase | Name of vaccine | Age | Number of participants | micrograms per dose | Neutralizing antibody responses (N%, CI) | Clinical Trial identifier |
|-----|--------|------|----------------------|-----------------|-----|----------------------|-------------------|------------------------------------------|--------------------------|
| [32] | Zhiwei Wu (2021) | China | Phase 1, 2 | CoronaVac | 60-64 | 36 | 1.5 μg | 34 (94%)[81.3-99.3] | NCT04383574 |
| [32] | Zhiwei Wu (2021) | China | Phase 1, 2 | CoronaVac | 65-69 | 35 | 1.5 μg | 29 (82.9%)[66.4-93.4] | NCT04383574 |
| [32] | Zhiwei Wu (2021) | China | Phase 1, 2 | CoronaVac | ≥70 | 26 | 1.5 μg | 25 (96%)[80.4-99.9] | NCT04383574 |
| [33] | Bihua Han (2021) | China | Phase 1, 2 | CoronaVac | 35-46 | 46 | 1.5 μg | 46 (100%)[92.3-100.0] | NCT4551547 |
| [33] | Bihua Han (2021) | China | Phase 1, 2 | CoronaVac | 6-11 | 69 | 1.5 μg | 48 (98.6%)[92.2-100.0] | NCT4551547 |
| [33] | Bihua Han (2021) | China | Phase 1, 2 | CoronaVac | 12-17 | 71 | 1.5 μg | 66 (93%)[84.3-97.7] | NCT4551547 |
| [5] | Shengli Xia (2020) | China | Phase 1, 2 | BBIBP-CorV | 18-59 | 24 | 2 μg | 24 (100%)[74.9-99.9] | NCT4352608 |
| [5] | Shengli Xia (2020) | China | Phase 1, 2 | BBIBP-CorV | ≥60 | 23 | 2 μg | 21 (91.30%)[71.1-97.8] | NCT4352608 |
| [5] | Shengli Xia (2020) | China | Phase 1, 2 | BBIBP-CorV | 6-12 | 84 | 2 μg | 80 (95.23%)[88.9-98.2] | NCT4352608 |
| [5] | Shengli Xia (2020) | China | Phase 1, 2 | BBIBP-CorV | 13-17 | 83 | 2 μg | 83 (100%)[91.2-100] | NCT4352608 |
| [5] | Yanjun Zhang (2020) | China | Phase 1, 2 | CoronaVac | 18-59 | 117 | 3 μg | 114 (97.4%)[92.7-99.5] | NCT4352608 |
| [34] | Tanriover (2021) | Turkey | Phase 3 | CoronaVac | 18-59 | 387 | 3 μg | 356 (91.98%)[88.8-94.3] | NCT4691908 |

Analysis V.2) software.

4) Clinical trial studies in phases 2 and 3.

The following studies were ruled out: 1) Duplicated studies. 2) Non-relevant articles. 3) Abstracts, letters, or review studies. 4) Studies published in languages other than English. 5) Articles with no access to the full text.
### Table 2

Event rates of neutralizing antibody responses to live attenuated SARS-CoV-2 among the participant 28 days after the second dose by micrograms per dose.

| Micrograms per dose | Author | Age | Number of participants | Neutralizing antibodies (N%) | Event rates |
|---------------------|--------|-----|------------------------|-------------------------------|-------------|
| 1.5 μg group (28 days) | Healthy individuals aged 60 years and older | [32] Zhiwei Wu (2021) | 60-64 | 36 | 34 (94.4%; 81.3–99.3) | 90.4% (78.2–96.1) |
| 2 μg group (28 days) | Healthy individuals aged 3–17 years and older | [33] Bihua Han (2021) | 3-5 | 46 | 46 (100.0%; 92.3–100.0) | 93.0% (80.0–98.3) |
| 3 μg group (28 days) | Healthy individuals aged 18 years and older | [14] Mine Durusu Tanriverdi (2021) | 18-59 | 387 | 356 (91.98%; 88.4–94.3) | 93.8% (91.6–95.4) |
| 4 μg group (28 days) | Healthy individuals aged 3–17 years | [32] Zhiwei Wu (2021) | 60-64 | 37 | 35 (94.6%; 81.8–99.3) | 96.7% (90.9–98.9) |
| 6 μg group (28 days) | Healthy individuals aged 60 years and older | [32] Zhiwei Wu (2021) | 60-64 | 38 | 38 (100.0%; 90.8–100.0) | 98.3% (94.2–99.5) |
| 8 μg group (28 days) | Healthy individuals aged 3–17 years and older | [32] Zhiwei Wu (2021) | 3-5 | 82 | 75 (83.2–95.9) | 94.5% (88.9–97.1) |

4. Discussion

Once herd immunity was developed in the general population, vaccination was regarded as a powerful and strategic approach for the control of the COVID-19 pandemic [13]. Research and development groups and institutes around the world had introduced a myriad of vaccine platforms, such as vector-based, mRNA-based, and inactivated virus vaccines and their overall efficacy in each category of vaccine remains to be fully elucidated [14].

Conventional vaccinations, such as the influenza vaccine, are usually based on the platform of inactivated viruses [15]. Because of its long and successful history of usage, the production of inactivated vaccines is considered a reliable vaccine production approach. Besides, it offers a cost-effective, and simple procedure of manufacture [16]. The inactivated viral vaccine has been shown to have high preventative effectiveness, stability, and feasibility in preservation and transportation [17]. The inactivated viruses lose their nucleic acid components and genetic machinery in the chemical or physical inactivation procedures, but they save the antigenic properties that render them immunogenic enough to elicit a functional immune response [18].

There are only several inactivated COVID-19 vaccines that are already being produced all around the world, and at least five have shown promise in preclinical and clinical examinations, leading to their approval for use. China produces the majority of the inactivated viral vaccine has been shown to have high preventative efficacy, stability, and feasibility in preservation and transportation [17]. The inactivated viruses lose their nucleic acid components and genetic machinery in the chemical or physical inactivation procedures, but they save the antigenic properties that render them immunogenic enough to elicit a functional immune response [18].

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antibody responses to SARS-CoV-2 among the participants 28 days after receiving the second dose by age and micrograms of doses. Our results demonstrated that the 6 μg-receiving groups had a trend for higher seroconversion than the other groups. Also, the overall prevalence of neutralizing antibody responses with a confidence interval of 95% and based on the random effect model was 71.27% (Q = 114.87) and with different ages and micrograms per dose was 95.50% (CI: 93.2–97.1%). Furthermore, our findings revealed that the outcomes of primary investigations are heterogeneous. According to the results of several trials involving numerous vaccines across three platforms, involving mRNA, viral vector, and inactivated virus, the vaccinations are successful in preventing SARS-CoV-2 infection in children and adults [21,22]. In addition, several inactivated COVID-19 candidate vaccines are currently being tested in clinical trials, and multiple studies have indicated that inactivated vaccines can generate neutralizing antibody responses and have favorable safety profiles [23–25].

A systematic review assessed the immunogenicity and efficacy of all SARS-CoV-2 vaccines; the front-runner vaccines, like as BNT162b2, mRNA-1273 a, rAd26/5, and ChAdOx-SARS-CoV-2 showed excellent induction of neutralizing antibody, T cell responses, and the associated ability to significantly limit the severe disease, hospitalization, and mortality [22]. A comprehensive review of the safety of SARS-CoV-2 vaccines in randomized controlled trials confirmed the safety of current COVID-19 vaccine platforms in mass vaccination, among them, the subjects receiving inactivated vaccines showed the fewest adverse events [20]. Other reviews have also evaluated the efficacy and safety of

![Fig. 2. the forest plot of Seroconversion rates of neutralizing antibody responses against SARS-CoV-2 among the participants 28 days after the second dose.](image-url)
the SARS-CoV-2 vaccines that are currently in clinical trials. Some of these studies report adverse effects in a series of cases compared to placebo groups [26,27]. The immunogenicity and safety of the CoronaVac inactivated vaccine in patients with certain baseline conditions such as HIV infection and malignancy have been evaluated elsewhere [28–30]. The outcomes of the current meta-analysis are somewhat in accordance with the findings of similar studies. McDonald et al. verified a moderate seroconversion in subjects receiving 3 and 6 μg doses of BBIBP and CoronaVac inactivated vaccines through a meta-analysis study [22]. Another meta-analysis demonstrated a high and moderate neutralizing antibody response following the administration of BBIBP and CoronaVac vaccines, respectively [31]. Data from our meta-analysis currently supports the immunogenicity of SARS-CoV2 inactivated vaccines at various doses in healthy subjects regardless of their age and this is the first meta-analysis on the association of the dose of inactivated SARS-CoV2 vaccine and antibody response. There were limitations to this meta-analysis such as the inclusion of the studies written only in English as well as a range of heterogeneity causatives such as age and dose differences. Furthermore, the amount of currently available material limited the scope of our analysis.

5. Conclusion

The rapid progress of vaccination programs was associated with some degree of doubt in public opinion that in some cases has led to irresponsible rumors. This study might provide new points of view ahead of healthcare systems and vaccine-reluctant individuals to draw a conclusion according to the current unbiased meta-analysis study regarding the effectiveness of inactivated vaccines in eliciting neutralizing and protective antibodies.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data relevant to the study are included in the article.

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Author’s contributions

Monireh Golphour, Tahoora Mousavi, and Alireza Mardomi designed and performed the literature search and collected the data. Reza Alizadeh-Navaei performed the statistical analysis, and all authors read and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare there is no conflict of interest.

Data availability

No data was used for the research described in the article.

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Not applicable.

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