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CLINICAL RESEARCH

Efficacy and safety of COVID-19 vaccines: a systematic review

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Abstract: Objective To evaluate systematically the efficacy and safety of COVID-19 vaccines. **Methods** PubMed, Embase, Cochrane Library, Clinicaltrial.gov, CNKI, Wanfang Data, China Biomedical Literature Service System, and China Clinical Trial Registry were searched for randomized controlled trials of COVID-19 vaccines published up to December 31, 2020. The Cochrane bias risk assessment tool was used to assess the quality of studies. A qualitative analysis was performed on the results of clinical trials. **Results** Thirteen randomized, blinded, controlled trials, which involved the safety and efficacy of 11 COVID-19 vaccines, were included. In 10 studies, the 28-day seroconversion rate of subjects exceeded 80%. In two 10,000-scale clinical trials, the vaccines were effective in 95% and 70.4% of the subjects, respectively. The seroconversion rate was lower than 60% in only one study. In six studies, the proportion of subjects who had an adverse reaction within 28 days after vaccination was lower than 30%. This proportion was 30%-50% in two studies and >50% in the other two studies. Most of the adverse reactions were mild to moderate and resolved within 24 hours after vaccination. The most common local adverse reaction was pain or tenderness at the injection site, and the most common systemic adverse reaction was fatigue, fever, or bodily pain. The immune response and incidence of adverse reactions to the vaccines were positively correlated with the dose given to the subjects. The immune response to the vaccines was worse in the elderly than in the younger population. In 6 studies that compared single-dose and double-dose vaccination, 4 studies showed that double-dose vaccination produced a stronger immune response than single-dose vaccination. **Conclusions** Most of the COVID-19 vaccines appear to be effective and safe. Double-dose vaccination is recommended. However, more research is needed to investigate the long-term efficacy and safety of the vaccines and the influence of dose, age, and production process on the protective efficacy.

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Key words: COVID-19; SARS-CoV-2; Vaccine; Systematic review; Efficacy; Safety; Clinical trial

It has been more than a year since the outbreak of the novel coronavirus pneumonia (COVID-19). Although the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that caused COVID-19 in China was effectively controlled, the global epidemic has not stopped. According to data from the World Health Organization, as of 16:05 on February 15,2021, Central European Time, the cumulative number of confirmed COVID-19 cases worldwide reached 108,579,352, and the cumulative deaths reached 2,396,408[1]. The COVID-19 epidemic as a major global public health event has become the primary health threat for all mankind, and impacted the world's political, economic and cultural greatly[2-3]. SARS-CoV-2 is a β-coronavirus with RNA as genetic material, which enters cell through a spike protein combined with angiotensin converting enzyme 2[4-5]. COVID-19 generally manifests as fever and dry cough, and injuries multiple organ, especially the lungs[2,5-6]. Wearing mask and maintaining social distancing have been confirmed as the most effective measures to stop the spread of the virus form China's experience of fighting the epidemic[3,7-9], and isolation and symptomatic supportive treatment still dominate

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for COVID-19 patients[5]. However, the efficacy of antiviral drugs and traditional Chinese medicines needs more evidence[10-11]. Due to the low penetration rate of masks and the limitations of treatment options abroad[12-13], more and more hopes are pinned on the development of a COVID-19 vaccine. According to different targets and technologies, vaccines can be divided into the following categories: inactivated vaccines, recombinant spike protein vaccines, viral vector vaccines, RNA vaccines, live attenuated vaccines and virus-like particle vaccines, etc[14-16]. Currently, hundreds of COVID-19 candidate vaccine projects have been registered in the US clinical trial database (clinicaltrials.gov)[15,17]. Results of phase 3 clinical trials of several vaccines are published[18-22]. As of January 1, 2021, China, Russia, the United States, Britain and other countries have approved their own mass vaccination plans for the population. This study evaluated the safety and effectiveness of the COVID-19 vaccine through systematic literature review and qualitative analysis for the published COVID-19 vaccine clinical trial results.

1 Information and methods

This systematic review was completed in accordance with the guidelines in the "Preferred Reporting Project for Systematic Evaluation and Meta-Analysis (PRISMA)"[23-24].

1.1 Literature inclusion criteria

The literature inclusion criteria: (1) The healthy men or non-pregnant women aged 18 and above; (2) COVID-19 vaccination as the intervention measure; (3) The randomized, controlled, and blinded trials; (4) The clinical trial results indicators include at least one or more as following: local adverse reactions (pain, itching, redness, swelling and induration, etc.), systemic adverse reactions (fever, diarrhea, fatigue, nausea/vomiting, etc.), the last vaccine neutralizing antibody geometric mean titer (GMT), seroconversion rate and other laboratory test indicators measured by live virus neutralization test 14 days or 28 days after inoculation.

1.2 Literature exclusion criteria

Documents that meet one of the following conditions were excluded: (1) Medical news, popular science articles, non-medical papers, reviews, letters, comments, basic research, case reports, conference abstracts; (2) No full text or literature published in a third language other than Chinese and English; (3) One of overlapping two studies were excluded; (4) If the data of the literature included in the later published literature, The former was excluded.

1.3 Literature search

The English databases PubMed, Embase, Cochrane Library and clinicaltrials.gov databases were searched. The Chinese databases searched included CNKI, Wanfang Database, China Biomedical Literature Service System and China Clinical Trial Registration Center. In order to ensure the comprehensiveness of the search results, this system evaluation used Boolean logic to search by “subject words + free words”. The main search terms include: COVID-19, 2019-nCoV, SARS-CoV-2, 2019 novel coronavirus, vaccines, vaccination, COVID-19 vaccines, mRNA-1273 vaccine, Ad5-nCoV vaccine, ChAdOx1 COVID-19 vaccine, BNT162 vaccine, controlled clinical trial, randomized controlled trials, controlled clinical trial, random, blind, placebo, trial, Meta, and etc. Chinese search terms include: 新型冠状病毒、新冠肺炎、新型冠状病毒肺炎、疫苗、试验、随机对照试验、随机对照研究、随机对照、随机、元分析、Meta、荟萃 , etc.

1.4 Literature screening and data extraction

The literature screening and data extraction were done independently by two researchers. Differences in the summary of the results will be discussed and dealt with by the two researchers or the third researcher. All results obtained in the database were imported into Note Express (Wuhan University Library Edition) software, and duplicate documents were removed mechanically using the software's duplicate check function. The initial screening by reading the title and abstract, and the secondary screening by reading the full text were completed. The extracted data included:

the first author, vaccine type, inoculation dose, interval between inoculations, number of subjects and baseline characteristics (race, sex ratio, age range or average age), research design, local and systemic adverse reactions, laboratory indicators, as well as funds, sponsors and registration number.

1.5 Methodological quality evaluation

Assess the risk of bias according to the Cochrane Systematic Review Manual[25-26].

1.6 Statistical analysis

The main results of this systematic review included the safety and effectiveness of the vaccine. Indicators for evaluating safety included local adverse reactions (pain, itching, redness, induration, etc.) and systemic adverse reactions (cough, diarrhea, fatigue, fever, headache, nausea/vomiting, itching, muscle pain, joint pain/discomfort, anorexia, etc.). The immunogenicity indicators included GMT, seroconversion rate, and the response of IgG or other specific antibodies to the receptor binding domain.

2 Results

2.1 Literature search results

There were 753 relevant articles published before December 31, 2020. After screening, 13 papers were included in the system evaluation[19-22,27-35]. The process of document screening was shown in Figure 1.

2.2 Methodological quality evaluation

The 13 included studies all adopted a randomized control method[19-22,27-35], with a double-blind method in 10 studies[21-22,27-32,34-35], and a single-blind method in 2 studies[20,33], and bothsingle-blind method and double-blind methodin one study[19]. All trials hid the allocation plan. Nine trials had incomplete data or selective reports[19,22,27,29-31,33-35], of which 2 had more missing data in the preprint[22,29], and the remaining 7 missed individual data[19,27,30-31,33-35]; 9 trials had other types of bias[19-20,22,29-32,34-35], for example, Keech et al.[30] did not perform virus neutralization test in the experimental design. In general, the included literature had a low risk of bias (Figure 2 & Table 1).

2.3 The characteristics of the included studies

The 13 included studies were randomized, blinded, and controlled trials, involving 5 inactivated vaccines[21-22,27-29,34], 2 recombinant spike protein vaccines[30,32], 2 RNA vaccines[20,31,33] and 2 adenovirus vector vaccines[19,35]. Table 2 for details of vaccine characteristics and developer information). There were 6 studies comparing the effects of single-dose and double-dose vaccination[19,27,30-31,33,35]. Most of the 13 studies compared the difference of two doses of vaccine at intervals of 2, 3 or 4 weeks. Most studies also compared the difference between low, medium and high injection doses. Participants in all trials were adults, and 5 articles reported the results of vaccines in the elderly population[19-20,32-33,35]. The baseline characteristics of the participants were shown in Table 3.

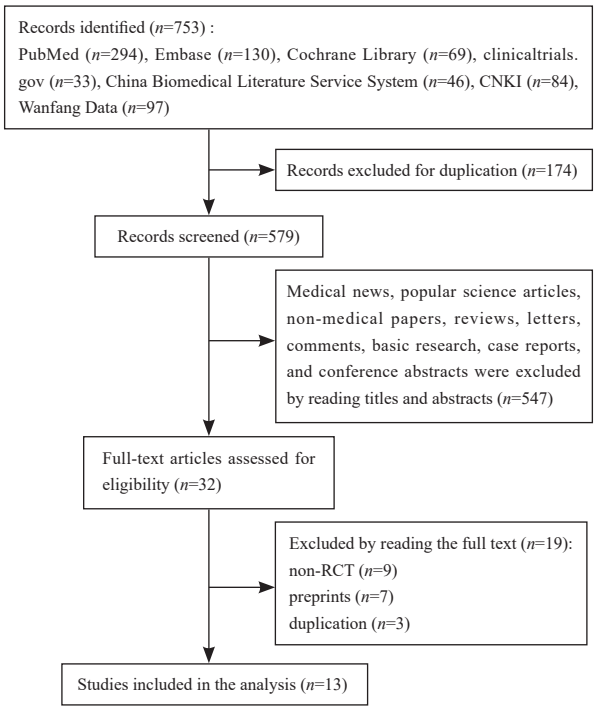

Figure 1 A flow diagram of literature screening

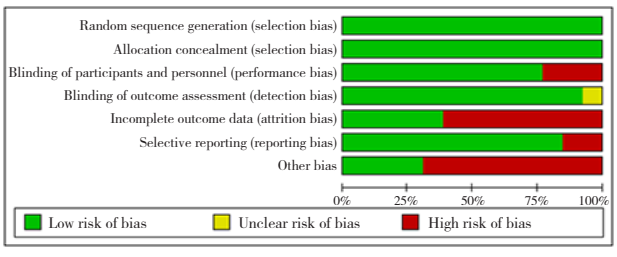

Figure 2 Risk assessment of literature bias

Table 1 Methodological quality evaluation of included studies

Studies	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Voysey 2021[19]	low risk	low risk	high risk	low risk	high risk	low risk	high risk
Polack 2020[20]	low risk	low risk	high risk	low risk	low risk	low risk	high risk
Xia 2020[21]	low risk	low risk	low risk	low risk	low risk	low risk	low risk
Pu 2020[22]	low risk	low risk	low risk	low risk	high risk	low risk	high risk
Xia 2021[27]	low risk	low risk	low risk	low risk	high risk	low risk	low risk
Che 2020[28]	low risk	low risk	low risk	low risk	low risk	low risk	low risk
Ella 2020[29]	low risk	low risk	low risk	low risk	high risk	low risk	high risk
Keech 2020[30]	low risk	low risk	low risk	unclear	high risk	low risk	high risk
Mulligan 2020[31]	low risk	low risk	low risk	low risk	high risk	low risk	high risk
Richmond 2020[32]	low risk	low risk	low risk	low risk	low risk	low risk	high risk
Walsh 2020[33]	low risk	low risk	high risk	low risk	high risk	low risk	low risk
Zhang 2021[34]	low risk	low risk	low risk	low risk	high risk	high risk	high risk
Zhu 2020[35]	low risk	low risk	low risk	low risk	low risk	high risk	high risk

Table 2 Experimental design and developers of the included studies

Studies	Vaccines	Adjuvant	Research type	Phase	Developers	Registration ID
Voysey 2021[19]	Adenovirus recombinant vector vaccine (ChAdOx1 nCoV-19/AZD1222)	No	Randomized double /single blind control	I/II/III	AstraZeneca	NCT04324606, NCT04400838, NCT04444674
Polack 2020[20]	RNA vaccine (BNT162b2)	Lipid nanoparticle	Randomized single-blind control	II/III	BioNTech / Pfizer	NCT04368729
Xia 2020[21]	Inactivated vaccine	Aluminum hydroxide	Randomized double-blind control	I/II	Wuhan Institute of Biological Products Co. Ltd	ChiCTR2000031809
Pu 2020[22]	Inactivated vaccine	Aluminum hydroxide	Randomized double-blind control	I	Institute of Medical Biology, Chinese Academy of Medical Sciences	NCT04412538
Xia 2021[27]	Inactivated vaccine (BBIBP-CorV)	Aluminum hydroxide	Randomized double-blind control	I/II	Beijing Institute of Biological Products	ChiCTR2000032459
Che 2020[28]	Inactivated vaccine	Aluminum hydroxide	Randomized double-blind control	II	Institute of Medical Biology, Chinese Academy of Medical Sciences	NCT04412538
Ella 2020[29]	Inactivated vaccine (BBV152)	Algel-IMDGor Algel	Randomized double-blind control	I	Bharat Biotech	NCT04471519
Keech 2020[30]	Recombinant spiroprotein nanoparticle vaccine (NVX-CoV2373)	Mareix-m1	Randomized double-blind control	II	Novavax	NCT04368988
Mulligan 2020[31]	RNA vaccine (BNT162b1)	Lipid nanoparticle	Randomized double-blind control	I/II	BioNTech/Pfizer	NCT04368728
Richmond 2020[32]	Recombinant spiroprotein vaccine (SCB-2019)	ASO3 or CpG/ Alum	Randomized double-blind control	I	Clover Biopharmaceuticals	NCT04405908
Walsh 2020[33]	RNA vaccine (BNT162b1/ BNT162b2)	Lipid nanoparticle	Randomized single-blind control	I	BioNTech/ Pfizer	NCT04368728
Zhang 2021[34]	Inactivated vaccine	Aluminum hydroxide	Randomized double-blind control	I/II	SINOVAC BIOTECH CO.LTD.	NCT04352608
Zhu 2020[35]	Adenovirus type-5-vectored vaccine	No	Randomized double-blind control	II	Beijing Institute of Biotechnology and Citic Biological	NCT04341389

Table 3 Baseline characteristics of the participants

Studies	Age (years)	Male/Female (*n*)	Experimental group/control group (*n*)	Injected dose	Injection procedure***	Country/ethnic group
Voysey 2021[19]	≥18*	55,447/54,360	55,048/54,759	2.2×10^{10}, $(3.5\text{-}6.5)\times10^{10}$ or $(5\text{-}7.5)\times10^{10}$ virus particles	Single injection or (0, 28)	Brazilian, South African and British/White
Polack 2020[20]	52#/≥16	19,129/18,394	19,198/18,325**	30 μg	(0, 21)	American, Argentinian, Brazilian, South African, German, Turkish/White
Xia 2020[21]	41.2/18-59	120/200	240/80	2.5 μg, 5 μg or 10 μg	(0, 14), (0, 28) or (0, 56)	Chinese/Asian
Pu 2020[22]	18-59*	unclear	144/48	50 EU, 100 EU or 150 EU	(0, 14) or (0, 28)	Chinese/Asian
Xia 2021[27]	53.7/≥18	301/339	470/170	2 μg, 4 μg or 8 μg	(0, 28)	Chinese/Asian
Che 2020[28]	41.4/18-59	258/486	595/149	100 EU or 150 EU	(0, 14) or (0, 28)	Chinese/Asian
Ella 2020[29]	18-55*	unclear	297/73	3 μg or 6 μg	(0, 14)	Indian/unclear
Keech 2020[30]	30.8/18-59	63/62	102/23	5 μg or 25 μg	(0, 21)	Australian /White
Mulligan 2020[31]	35.4/18-55	23/22	36/9	10 μg, 30 μg or 100 μg	Single injection or (0, 21)	German/ White
Richmond 2020[32]	35.7/18-75	70/78	118/30	3 μg, 9 μg or 30 μg	(0, 21)	Australian/White
Walsh 2020[33]	35.9/18-85	94/101	156/39	10 μg, 20 μg, 30 μg or 100 μg	Single injection or (0, 21)	American/White
Zhang 2021[34]	42.6/18-59	345/389	568/166	3 μg or 6 μg	(0, 14) or (0, 28)	Chinese/Asian
Zhu 2020[35]	39.7/≥18	445/445	382/508	5×10^{10} or 1×10^{11} virus particles	Single injection	Chinese/Asian

* The study did not report a mean age; # The median age; ** Only the data of subjects without any evidence of SARS-CoV-2 infection before vaccination were selected; *** The numbers in parentheses indicate when vaccine was injected, for example (0, 28) means that the vaccine is injected again on the 28th day after the first injection.

2.4 Qualitative analysis

2.4.1 The effectiveness and safety of vaccines

In 10 studies, the 28-day seroconversion rate of testee exceeded 80%[21-22,27-34]. The RNA vaccine (BNT162b2) reported by Polack achieved 95% efficiency[20], the recombinant adenovirus vector vaccine (ChAdOx1 nCoV-19) reported by Voysey achieved an effective rate of 70.4%[19], but Zhu reported that the 28-day seroconversion rate of the adenovirus recombinant vector vaccine in testee was less than 60%[35].

In 6 studies, the incidence of adverse reactions in volunteers within 28 days for vaccination was less than 30%[20-22,27-28,34]. The adverse reaction rates of the recombinant spike protein vaccine (SCB-2019) reported by Richmond[32] and the RNA vaccine reported by Walsh[33] were 34.7% and 39.1%, respectively, and the adverse reaction rates of the RNA vaccine (BNT162b1) reported by Mulligan[31] and the adenovirus recombinant vector vaccine reported by Zhu[35] were 52.8% and 73.0%, respectively. Three studies could not obtain the adverse reaction rate[19,29-30]. The adverse reactions of all vaccinated testee were mostly mild to moderate, and could be relieved within 24 hours after vaccination. The most common local adverse reaction included pain or tenderness at the injection site[19-22,27-35]. Fatigue was reported as the most common systemic adverse reaction in 9 studies[19-20,22,28-29,31,33-35]. In addition, fever was reported as the most common systemic adverse reaction in 2 studies[21,27], and 2 studies reported somatic pain as the most common systemic adverse reaction[30,32] (Table 4).

2.4.2 Dose difference

The difference in injection dose is an important factor affecting the immunogenicity and safety of the vaccine. A total of 9 studies[21-22,27-29,32-35] found significant differences in GMT and seroconversion rates obtained from testee with different doses of vaccination, 8 of which[20-22,28-29,31,34-35] found that GMT increased, and 4[22,28-29,32] found that the seroconversion rate of testee increased with the increase of vaccine dose, but the incidence of adverse reactions also increases relatively [22,28-29,32]. Therefore, when the clinical trial entered Phase III, the researchers set the medium dose as the standard dose of the vaccine [19-20].

Table 4 Effectiveness and safety of vaccines

Studies	Key effectiveness indicators	Total incidence of adverse reactions [%(*n*/*N*)]	Incidence of serious adverse reactions [%(*n*/*N*)]	The most common adverse reactions	
				Local reactions	Systemic reactions
Voysey 2021[19]	Efficacy 70.4%*	Unclear	0.15 (84/55,048)	Pressing pain	fatigue
Polack 2020[20]	Efficacy 95%**	27.0%#	Unclear	Pain	Fatigue
Xia 2020[21]	Day 14 seroconversion rates: 97.6% in the middle dose group; Day 14 GMT: 121 in the standard dose group	15.0(36/240)	0(0/240)	Pain	Fever
Pu 2020[22]	Day 28 seroconversion rates: 80%, 96% and 92% in the low dose, middle dose and high dose groups respectively; Day 28 GMT: 10.6, 15.4 and 19.6 in the low dose, middle dose and high dose groups respectively	25.7(37/144)	0(0/144)	Pain	Fatigue
Xia 2021[27]	Day 28 seroconversion rates: 100% each in the low dose, middle dose and high dose groups; Day 28 GMT: 13.4, 18.9 and 23.7 in the low dose, middle dose and high dose groups respectively	29.2(42/144)	0(0/144)	Pain	Fever
Che 2020[28]	Day 28 seroconversion rates: 92% in the middle dose group and 96% in the high dose group; Day 28 GMT: 19 in the middle dose group and 21 in the high dose group	24.5(146/595)	0(0/595)	Pain	Fatigue
Ella 2020[29]	Day 28 seroconversion rates: 87.9% in the low dose group and 91.9% in the high dose group; Day 28 GMT: 61.7 in the low dose group and 66.4 in the high dose group	Unclear	Unclear	Pain	Fatigue
Keech 2020[30]	Day 35 GMT: 4-6 times higher than that of serum in convalescent period	Unclear	1.96(2/102)	Pressing pain	Arthralgia
Mulligan 2020[31]	Day 28 GMT: 168 in the low dose group and 267 in the middle dose group	52.8(19/36)	5.6(2/36)	Pain	Fatigue
Richmond 2020[32]	Day 36 seroconversion rates: 95%, 100% and 100% in the low dose, middle dose and high dose groups respectively	34.7(41/118)	1.69(2/118)	Pain	Headache
Walsh 2020[33]	Day 28 GMT (BNT162b1 vaccine): 168, 167 and 267 in the low dose, middle dose and high dose groups respectively; Day 28 GMT (BNT162b2 vaccine): 157, 263 and 361 in the low dose, middle dose and high dose groups respectively	39.1(61/156)	4.49(7/156)	Pain	Fatigue
Zhang 2021[34]	Day 28 seroconversion rates: 25% in the low dose group and 83% in the high dose group; Day 28 GMT: 5.4 in the low dose group and 15.2 in the high dose group	26.6(151/568)	1.04(1/96)	Pain	Fatigue
Zhu 2020[35]	Day 28 seroconversion rates: 59% in the low dose group and 47% in the standard dose group; Day 28 GMT: 18.3 in the low dose group and 19.5 in the standard dose group	73.0(279/382)	6.5(25/382)	Pain	Fatigue

GMT: geometric mean titers; * The efficacy is calculated from the corrected relative risk; ** Efficacy =100×(1-IRR), IRR is the ratio of the number of confirmed COVID-19 cases per 1000 person-years of follow-up in the vaccine group to the corresponding cases in the placebo group; # The original literature only gave the incidence of adverse reactions, but did not give the specific number of people.

2.4.3 Difference of age Four studies specifically recruited the elderly 60 years and older, and conducted a special subgroup analysis in the results. Richmond [32] reported that the GMT range measured by the micro-neutralization test in the elderly group was 1567-3625, which was lower than 2510-4452 in the 18-59-year-old group. The incidence of systemic adverse reactions in the elderly after the first injection was 17%, which was lower than 38% in the 18-59 years-old group. Xia [27] also reported that the GMT of the elderly group was lower than that of the 18-59 years-old group, and the seroconversion time was later than that of the 18-59 years-old group. The incidence of systemic adverse reactions in the elderly within 7 days after vaccination was 28.6%, which was lower than 41.7% of the 18-59 years-old group. Polack[20] and Walsh[33] also reported similar results. In short, compared with healthy people aged 18 to 59, the GMT detected in the serum was significantly lower in elderly population vaccinated with the same vaccine according to the same procedure, but the incidence of adverse reactions in the elderly population was also significantly lower [20,27,32-33].

2.4.4 Differences in vaccination procedures

Although a number of studies designed a comparison of different vaccination procedures, the results of the experiment were complicated. Zhang 's research showed that testee who vaccinated at 2-week intervals got a faster immune response, but a stronger immune response at 4-week intervals[34]. Che detected a stronger immune response in testee who were vaccinated at 2-week intervals[28]. Xia also found that the incidence of adverse reactions in testee vaccinated at 2-week intervals was lower than that at 4-week intervals[21]. In 6 studies that compared single-dose and double-dose vaccination, 4 studies showed that double-dose vaccination produced a stronger immune response than single-dose vaccination[19,31,33,35].

2.4.5 Differences of vaccine type

The RNA vaccine (BNT162b2) reported by Polack[20] and the recombinant adenovirus vector vaccine (ChAdOx1 nCoV-19) reported by Voysey[19] involved more than 10,000 people, and two both used relative risk to calculate the effective rate, showing that effective rate of the former was 95%[20], and the latter was 70.4%[19]. Owing to differences in the design, the small sample size, and different outcome indicators of other clinical trials, their effective rates were not yet comparable.

3 Discussion

The system evaluation draws the following conclusions: (1) All candidate vaccines have a good immunogenicity and safety except the vaccine reported by Zhu[35]. Within 28 days after vaccination, the testee' serum GMT increased significantly, and the seroconversion rate was mostly greater than 80%. The adverse reaction rate of most vaccines was less than 30%, degree was mild to moderate, and symptoms were alleviated within 24 hours. (2) The potency and adverse reaction rate after vaccination were positively related to the dose. Most clinical trials chose the middle dose when the phase III. This might be the result of comprehensive consideration of effectiveness and safety. (3) Under the same conditions, the vaccine had poor immunogenicity to elderly people over 60, but the adverse reaction rate was also low. One of the possible reasons was low immunity of the older. A lot of studies on the tolerance of the elderly population to the vaccine still are needed. In addition, there are currently no published results of clinical trials targeting juveniles. (4) Most studies recommend double-dose vaccination, but the interval needs further study.

However, this systematic review has some limitations: (1) No evidence of the long-term effectiveness and safety of the vaccine. Due to the urgency of vaccine development, most trials only followed up to 28 days after vaccination. Whether neutralizing antibodies can be maintained for a long time and whether there are delayed adverse reactions after vaccination still require a longer period. (2) In order to get more up-to-date evidence, this systematic review also includes preprinted documents, which have not been peer reviewed and some of the data are not available. (3) Only randomized, double-blind, and controlled trials were included, while observational studies, retrospective case analysis, and early animal experiments were all excluded. For example, an open label trial conducted by Anderson[36] found that mRNA-1273 vaccine had a good safety in the elderly population. Logonov[37] reported two adenovirus recombinant vector vaccine preparations (rAd26) in a non-random clinical trial (rAd26-S and rAd5-S) had a good safety and immunogenicity in healthy people aged 18 to 60. (4) There were differences in the design of various clinical trials, which made it impossible to compare the advantages and disadvantages of different types of vaccines. For example, Voysey[19] and Polack[20] used relative risk to calculate the effective rate. Although the remaining 10 studies have completed the virus neutralization test, the experimental design schemes were quite different [21-22,27-29,31-35]. (5) Only Chinese and English documents were searched in this systematic review, and documents published in other languages such as Japanese and French were excluded.

In conclusion, this systematic review summarized the results of clinical trials related to the COVID-19 vaccine, showing that most vaccines had a good safety and effectiveness. It is believed that with the widespread vaccination of COVID-19, it is possible to control and end the global pandemic of COVID-19.

Conflict of interest: The authors have no conflicts of interest to disclose.

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论著·临床研究

COVID-19 疫苗的有效性和安全性的系统评价

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［摘要］　**目的**　系统评价新型冠状病毒肺炎（COVID-19）疫苗的有效性和安全性。**方法**　通过计算机检索有关 COVID-19 疫苗的临床随机对照试验文献，对临床试验结果进行定性分析。检索时间为各数据库建库至 2020 年 12 月 31 日。所检索的数据库包括 PubMed、Embase、Cochrane 图书馆、Clinicaltrial.gov、中国知网、万方数据、中国生物医学文献服务系统和中国临床试验注册中心。使用 Cochrane 偏倚风险评估工具评估文献质量。**结果**　纳入了 13 项随机、盲法、对照试验，涉及 11 种 COVID-19 疫苗接种的安全性和有效性。在其中 10 项研究中，受试者的 28 d 血清转化率超过 80%；2 项万人规模的临床试验中，分别取得了 95% 和 70.4% 的有效率；1 项研究的血清转化率低于 60%。在对接种后 28 d 内不良反应发生率的分析显示，6 项研究不良反应发生率低于 30%，2 项研究为 30%~50%，2 项研究高于 50%。在 13 项研究中，疫苗接种不良反应事件绝大部分为轻度到中度，在接种后 24 h 内缓解；最常见的局部不良反应为注射部位疼痛或压痛，最常见的系统性不良反应为疲劳、发热或躯体痛。受试者对疫苗的免疫反应和不良反应发生率与接种剂量呈正相关。老年人对疫苗的免疫反应较年轻人差。6 项研究比较了疫苗单剂量与双剂量接种的效应，其中 4 项研究显示双剂量接种比单剂量接种产生更强的免疫反应。**结论**　大部分 COVID-19 疫苗具有较好的有效性和安全性；推荐双剂量接种。然而 COVID-19 疫苗的长期有效性、安全性及剂量、年龄和工艺差异对保护效力的影响需要更多的研究证实。

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［关键词］　新型冠状病毒肺炎；严重急性呼吸综合征冠状病毒 2；疫苗；系统评价；有效性；安全性；临床试验

Efficacy and safety of COVID-19 vaccines: a systematic review

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Abstract: Objective　To evaluate systematically the efficacy and safety of COVID-19 vaccines. **Methods**　PubMed, Embase, Cochrane Library, Clinicaltrial.gov, CNKI, Wanfang Data, China Biomedical Literature Service System, and China Clinical Trial Registry were searched for randomized controlled trials of COVID-19 vaccines published up to December 31, 2020. The Cochrane bias risk assessment tool was used to assess the quality of studies. A qualitative analysis was performed on the results of clinical trials. **Results**　Thirteen randomized, blinded, controlled trials, which involved the safety and efficacy of 11 COVID-19 vaccines, were included. In 10 studies, the 28-day seroconversion rate of subjects exceeded 80%. In two 10 000-scale clinical trials, the vaccines were effective in 95% and 70.4% of the subjects, respectively. The seroconversion rate was lower than 60% in only one study. In six studies, the proportion of subjects who had an adverse reaction within 28 days after vaccination was lower than 30%. This proportion was 30%-50% in two studies and >50% in the other two studies. Most of the adverse reactions were mild to moderate and resolved within 24 hours after vaccination. The most common local adverse reaction was pain or tenderness at the injection site, and the most common systemic adverse reaction was fatigue, fever, or bodily pain. The immune response and incidence of adverse reactions to the vaccines were positively correlated with the dose given to the subjects. The immune response to the vaccines was worse in the elderly than in the younger population. In 6 studies that compared

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single-dose and double-dose vaccination, 4 studies showed that double-dose vaccination produced a stronger immune response than single-dose vaccination. **Conclusions** Most of the COVID-19 vaccines appear to be effective and safe. Double-dose vaccination is recommended. However, more research is needed to investigate the long-term efficacy and safety of the vaccines and the influence of dose, age, and production process on the protective efficacy.

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Key words: COVID-19; SARS-CoV-2; Vaccine; Systematic review; Efficacy; Safety; Clinical trial

新型冠状病毒肺炎（COVID-19）疫情暴发至今已 1 年余。虽然 COVID-19 疫情在我国已经得到了有效控制，但全球整体疫情形势依然严峻。根据世界卫生组织的数据，截至欧洲中部时间 2021 年 2 月 15 日 16:05，全球累计 COVID-19 确诊病例达到 108 579 352 例，累计死亡人数达到 2 396 408 人[1]。作为全球的重大公共卫生事件，COVID-19 疫情成为全人类首要的健康威胁，世界政治经济文化也受到巨大冲击[2-3]。导致 COVID-19 的严重急性呼吸综合征冠状病毒 2（SARS-CoV-2）是以 RNA 为遗传物质的 β 属冠状病毒，通过刺突蛋白结合血管紧张素转化酶 2 进入细胞[4-5]。COVID-19 患者的首发症状以发热和干咳多见，在多脏器损伤中，肺脏受损最为严重[2,5-6]。在疫情控制上，佩戴口罩和保持社交距离已经在中国抗击疫情的实践中被确认为阻断病毒传播最为有效的措施[3,7-9]。在对 COVID-19 患者的治疗上，隔离和对症支持治疗仍占主要地位[5]，而关于抗病毒药物和中药等的疗效还需更多证据的支持[10-11]。由于口罩在国外普及率的低下和治疗方案的局限性[12-13]，越来越多的希望被寄托在 COVID-19 疫苗的开发上。根据靶点和技术的不同，疫苗可以被分为以下几类：灭活疫苗、重组刺突蛋白疫苗、病毒载体疫苗、RNA 疫苗、减毒活疫苗和病毒样颗粒疫苗等[14-16]。目前，已有数百项 COVID-19 候选疫苗的项目在美国临床试验数据库（clinicaltrials.gov）注册[15,17]，数种疫苗的 3 期临床试验结果予以发表[18-22]。截至 2021 年 1 月 1 日，中、俄、美、英等国家先后批准了本国疫苗在人群中的大规模接种计划。本研究通过系统文献复习及定性分析已发表的 COVID-19 疫苗临床试验结果，评估 COVID-19 疫苗的安全性与有效性。

1 资料与方法

本系统评价遵循《系统评价和 Meta 分析的首选报告项目（PRISMA）》中的准则完成[23-24]。

1.1 文献纳入标准

文献纳入标准包括：（1）试验对象为 18 岁及以上的健康男性或未孕女性；（2）干预措施为接种 COVID-19 疫苗；（3）试验类型为随机、对照、盲法试验；（4）临床试验结果指标至少包括以下一项或几项：局部不良反应（疼痛、瘙痒、发红、肿胀和硬结等）、全身不良反应（发热、腹泻、疲劳、恶心 / 呕吐等）、末次疫苗接种 14 d 或 28 d 后以活病毒中和试验测得的中和抗体几何平均滴度（GMT）、血清转化率及其他实验室检测指标。

1.2 文献排除标准

具备以下条件之一的文献被排除：（1）文献类型为医学新闻、科普文章、非医学类论文、综述、信件、评论、基础研究、病例报告、会议摘要；（2）无法获取全文或以中文、英文外的第三种语言发表的文献；（3）若两项研究的受试者存在重叠，则其中之一被排除；（4）若文献的数据被之后发表的文献包含在内，前者予以排除。

1.3 文献检索

对英文数据库 PubMed、Embase、Cochrane 图书馆和 clinicaltrials.gov 数据库进行了检索。检索的中文数据库包括中国知网、万方数据库、中国生物医学文献服务系统和中国临床试验注册中心。为了保证检索结果的全面性，本系统评价运用布尔运算逻辑，采取“主题词 + 自由词”方式进行了检索。主要检索词包括：COVID-19、2019-nCoV、SARS-CoV-2、2019 novel coronavirus、vaccines、vaccination、COVID-19 vaccines、mRNA-1273 vaccine、Ad5-nCoV vaccine、ChAdOx1 COVID-19 vaccine、BNT162 vaccine、controlled clinical trial、randomized controlled trials、controlled clinical trial、random、blind、placebo、trial、Meta 等。中文检索词包括新型冠状病毒、新冠肺炎、新型冠状病毒肺炎、疫苗、试验、随机对照试验、随机对照研究、随机对照、随机、元分析、Meta、荟萃等。

1.4 文献筛选和资料提取

文献筛选和资料提取工作由两位研究者独立完成。若结果汇总时出现分歧，由两位研究者讨论处理或交由第 3 位研究者决定。在数据库中获得的所有检索结果导入 NoteExpress（武汉大学图书馆版）软件中，使用软件的查重功能机械地去除重复文献。然后通过阅读标题和摘要完成初次筛选，通过阅读全文完成二次筛选。在第二次筛选中，每一篇文献被剔除的原因均被记录。所提取数据包括：第一作者、疫苗类型、接种剂量、接种间隔时间、受试者人数及基线特征（种族、性别比例、年龄范围或平均年龄）、研究设计方案、局部和全身不良反应、实验室检查指标，以及基金、赞助商和注册号等。

1.5 方法学质量评价

依据 Cochrane 系统评价手册评估偏倚风险 [25-26]。

1.6 统计学分析

本系统评价的主要结果包括疫苗的安全性和有效性。评估安全性的指标包括局部不良反应（疼痛、瘙痒、红肿、硬结等）及全身不良反应（咳嗽、腹泻、疲倦、发烧、头痛、恶心 / 呕吐、瘙痒、肌肉疼痛、关节痛 / 不适、厌食等）。评估免疫原性的指标包括 GMT、血清转化率、IgG 或其他特异性抗体对受体结合域的反应。

2 结果

2.1 文献检索结果

检索了截至 2020 年 12 月 31 日之前发表的所有相关文献，共得到 753 篇。经过筛选后纳入 13 篇 [19-22,27-35] 进入本系统评价。文献筛选的具体流程见图 1。

2.2 纳入研究的方法学质量评价

纳入的 13 项研究 [19-22,27-35] 均采用了随机对照的方法，其中 10 项 [21-22,27-32,34-35] 实施了双盲法，2 项 [20,33] 实施了单盲法，1 项 [19] 在不同试验地点分别使用了单盲法和双盲法；所有试验均隐藏了分配方案；9 项 [19,22,27,29-31,33-35] 数据不完整或选择性报告，其中 2 项 [22,29] 预印本缺失数据较多，其余 7 项 [19,27,30-31,33-35] 缺失个别数据；9 项 [19-20, 22, 29-32, 34-35] 存在其他类型偏倚，如 Keech 等 [30] 在试验设计中未做病毒中和试验。总的来讲，所纳入文献的偏倚风险较低。见图 2 和表 1。

2.3 纳入研究的基本特征

所纳入的 13 项研究均为随机、盲法、对照试验，共涉及灭活疫苗 5 种 [21-22, 27-29, 34]、重组刺突蛋白疫苗 2 种 [30,32]、RNA 疫苗 2 种 [20,31,33] 和腺病毒载体疫苗 2 种 [19,35]，疫苗特性、开发者等信息见表 2。有 6 项研究比较了疫苗单剂量与双剂量接种的效应 [19,27,30-31,33,35]。大部分研究比较了以 2 周、3 周或 4 周为间隔注射两剂疫苗的差别。大部分研究也比较了低、中、高不同注射剂量的差别。所有试验的参与者均为成年人，有 5 篇文献报道了疫苗在老年人群体中的结果 [19-20,32-33,35]。所纳入研究参与者的基线特征见表 3。

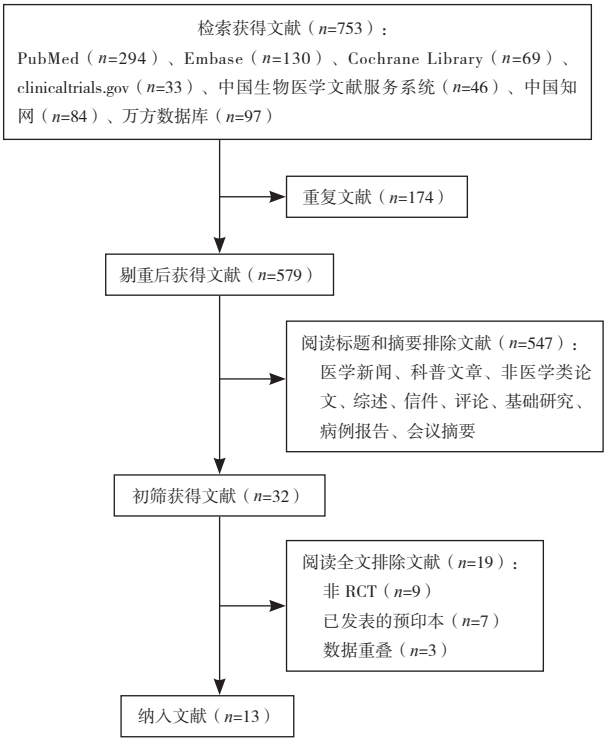

图 1 文献筛选流程图

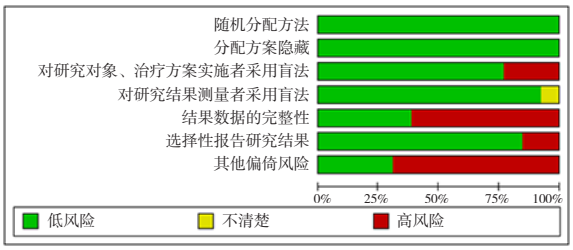

图 2 文献偏倚风险评估

表 1　纳入研究的方法学质量评价

研究	随机分配方法	分配方案隐藏	对研究对象、治疗方案实施者采用盲法	对研究结果测量者采用盲法	结果数据的完整性	选择性报告研究结果	其他偏倚风险
Voysey 2021[19]	低风险	低风险	高风险	低风险	高风险	低风险	高风险
Polack 2020[20]	低风险	低风险	高风险	低风险	低风险	低风险	高风险
Xia 2020[21]	低风险	低风险	低风险	低风险	低风险	低风险	低风险
Pu 2020[22]	低风险	低风险	低风险	低风险	高风险	低风险	高风险
Xia 2021[27]	低风险	低风险	低风险	低风险	高风险	低风险	低风险
Che 2020[28]	低风险	低风险	低风险	低风险	低风险	低风险	低风险
Ella 2020[29]	低风险	低风险	低风险	低风险	高风险	低风险	高风险
Keech 2020[30]	低风险	低风险	低风险	不清楚	高风险	低风险	高风险
Mulligan 2020[31]	低风险	低风险	低风险	低风险	高风险	低风险	高风险
Richmond 2020[32]	低风险	低风险	低风险	低风险	低风险	低风险	高风险
Walsh 2020[33]	低风险	低风险	高风险	低风险	高风险	低风险	低风险
Zhang 2021[34]	低风险	低风险	低风险	低风险	高风险	高风险	高风险
Zhu 2020[35]	低风险	低风险	低风险	低风险	低风险	高风险	高风险

表 2　纳入研究的试验设计和开发者

研究	疫苗	佐剂	研究类型	分期	开发者	注册号
Voysey 2021[19]	腺病毒重组载体疫苗 (ChAdOx1 nCoV-19/ AZD1222)	无	随机双盲 / 单盲对照	I/ II/ III	AstraZeneca	NCT04324606, NCT04400838, NCT04444674
Polack 2020[20]	RNA 疫苗 (BNT162b2)	脂质纳米粒	随机单盲对照	II/ III	BioNTech 公司和辉瑞公司	NCT04368729
Xia 2020[21]	灭活疫苗	氢氧化铝	随机双盲对照	I/ II	武汉生物制品研究所有限公司	ChiCTR2000031809
Pu 2020[22]	灭活疫苗	氢氧化铝	随机双盲对照	I	中国医学科学院医学生物研究所	NCT04412538
Xia 2021[27]	灭活疫苗 (BBIBP-CorV)	氢氧化铝	随机双盲对照	I/ II	北京生物制品研究所	ChiCTR2000032459
Che 2020[28]	灭活疫苗	氢氧化铝	随机双盲对照	II	中国医学科学院医学生物研究所	NCT04412538
Ella 2020[29]	灭活疫苗 (BBV152)	Algel-IMDG 或 Algel	随机双盲对照	I	Bharat 生物技术公司	NCT04471519
Keech 2020[30]	重组刺突蛋白纳米颗粒疫苗 (NVX-CoV2373)	mareix-m1	随机双盲对照	II	Novavax 公司	NCT04368988
Mulligan 2020[31]	RNA 疫苗 (BNT162b1)	脂质纳米粒	随机双盲对照	I/ II	BioNTech 公司和辉瑞公司	NCT04368728
Richmond 2020[32]	重组刺突蛋白疫苗 (SCB-2019)	ASO3 或 CpG/Alum	随机双盲对照	I	三叶草生物制药	NCT04405908
Walsh 2020[33]	RNA 疫苗 (BNT162b1/ BNT162b2)	脂质纳米粒	随机单盲对照	I	BioNTech 公司和辉瑞公司	NCT04368728
Zhang 2021[34]	灭活疫苗	氢氧化铝	随机双盲对照	I/ II	北京科兴生物制品	NCT04352608
Zhu 2020[35]	腺病毒 5 载体疫苗	无	随机双盲对照	II	北京生物技术研究所和中信生物	NCT04341389

表 3　纳入研究的基线特征

研究	年龄（平均 / 范围，岁）	男 / 女（例）	试验组 / 对照组（例）	注射剂量	注射程序 ***	国家 / 主要人种
Voysey 2021[19]	≥ 18*	55 447/54 360	55 048/54 759	2.2×10^{10}、$(3.5\sim6.5)\times10^{10}$ 或 $(5\sim7.5)\times10^{10}$ 病毒颗粒	单剂量或 (0, 28)	巴西、南非、英国 / 白人
Polack 2020[20]	52#/ ≥ 16	19 129/18 394	19 198/18 325**	30 μg	(0, 21)	美国、阿根廷、巴西、南非、德国及土耳其 / 白人
Xia 2020[21]	41.2/18~59	120/200	240/80	2.5 μg、5 μg 或 10 μg	(0, 14)、(0, 28) 或 (0, 56)	中国 / 亚洲人
Pu 2020[22]	18~59*	不详	144/48	50 EU、100 EU 或 150 EU	(0, 14) 或 (0, 28)	中国 / 亚洲人
Xia 2021[27]	53.7/ ≥ 18	301/339	470/170	2 μg、4 μg 或 8 μg	(0, 28)	中国 / 亚洲人
Che 2020[28]	41.4/18~59	258/486	595/149	100 EU 或 150 EU	(0, 14) 或 (0, 28)	中国 / 亚洲人
Ella 2020[29]	18~55*	不详	297/73	3 μg 或 6 μg	(0, 14)	印度 / 不详
Keech 2020[30]	30.8/18~59	63/62	102/23	5 μg 或 25 μg	(0, 21)	澳大利亚 / 白人
Mulligan 2020[31]	35.4/18~55	23/22	36/9	10 μg、30 μg 或 100 μg	单剂量或 (0, 21)	德国 / 白人
Richmond 2020[32]	35.7/18~75	70/78	118/30	3 μg、9 μg 或 30 μg	(0, 21)	澳大利亚 / 白人
Walsh 2020[33]	35.9/18~85	94/101	156/39	10 μg、20 μg、30 μg 或 100 μg	单剂量或 (0, 21)	美国 / 白人
Zhang 2021[34]	42.6/18~59	345/389	568/166	3 μg 或 6 μg	(0, 14) 或 (0, 28)	中国 / 亚洲人
Zhu 2020[35]	39.7/ ≥ 18	445/445	382/508	5×10^{10} 或 1×10^{11} 病毒颗粒	单剂量	中国 / 亚洲人

注：* 该研究未报道平均年龄；# 中位年龄；** 仅选取了接种前无任何 SARS-CoV-2 感染迹象的受试者的数据；*** 括号中的数字表示注射疫苗的时间，如（0，28）表示在第 1 次注射后，第 28 天再次注射。

2.4　定性分析结果

2.4.1　疫苗的有效性和安全性　在 10 项研究中，受试者的 28 d 血清转化率超过 80%[21-22, 27-34]；在两项万人规模的临床试验中，Polack 等 [20] 报道的 RNA 疫苗（BNT162b2）取得了 95% 的有效率，Voysey 等 [19] 报道的腺病毒重组载体疫苗（ChAdOx1 nCoV-19）取得了 70.4% 的有效率；Zhu 等 [35] 报道的腺病毒重组载体疫苗在受试者中的 28 d 血清转化率低于 60%。见表 4。

在 6 项研究中，志愿者在接种疫苗后的 28 d 内不良反应发生率低于 30%[20-22,27-28,34]；Richmond 等 [32] 报道的重组刺突蛋白疫苗（SCB-2019）和 Walsh 等 [33] 报道的 RNA 疫苗的不良反应率分别为 34.7% 和 39.1%；Mulligan 等 [31] 报道的 RNA 疫苗（BNT162b1）和 Zhu 等 [35] 报道的腺病毒重组载体疫苗的不良反应率分别为 52.8% 和 73.0%；3 项研究无法获取不良反应率 [19,29-30]。所有疫苗接种的受试者发生不良反应事件绝大部分都是轻度到中度，且在接种后 24 h 内可缓解；所有疫苗接种最常见的局部不良反应均为注射部位疼痛或压痛 [19-22,27-35]；疲劳在 9 项研究中被报道为最常见的系统性不良反应 [19-20,22,28-29,31,33-35]。此外，发热在 2 项研究中被报道为最常见的系统性不良反应 [21,27]，也有 2 项研究报道躯体痛为最常见的系统性不良反应 [30,32]。见表 4。

2.4.2　剂量差异的影响　注射剂量的不同是影响疫苗免疫原性和安全性的重要因素。共有 9 项研究 [21-22,27-29,32-35] 发现接受不同剂量疫苗接种的受试者获得的 GMT 和血清转化率存在显著性差异，其中 8 项 [20-22,28-29,31,34-35] 发现 GMT 随着疫苗剂量的增加而增加，4 项 [22,28-29,32] 发现受试者血清转化率随疫苗剂量的增加而增加。但随着接种剂量的加大，不良反应的发生率也相对增加 [22,28-29,32]。因此，当临床试验进入 III 期阶段，研究者将中等剂量设定为疫苗的标准剂量 [19-20]。

2.4.3　年龄差异的影响　有 4 项研究专门招募了 60 岁及以上的老年人群，并在结果中进行了专门的亚组分析。Richmond 等 [32] 报道使用微量中和试验在老年人组测得的 GMT 范围为 1 567~3 625，低于 18~59 岁组的 2 510~4 452；而老年人在第 1 次注射后的全身不良反应发生率为 17%，低于 18~59 岁组的 38%。Xia 等 [27] 也报道老年人组 GMT 低于

18~59 岁组，且达到血清转化时间晚于 18~59 岁组；而老年人在接种后 7 d 内的全身不良反应发生率为 28.6%，低于 18~59 岁组的 41.7%。Polack 等 [20] 和 Walsh 等 [33] 两项研究也报道了相似结果。总之，相比于 18~59 岁的健康人群，老年人群按照相同的程序接种同种疫苗后，血清中所检测到的 GMT 显著偏低，但相应地老年人群中不良反应发生率也显著偏低 [20,27,32-33]。

2.4.4 接种程序差异的影响　虽然多项研究设计了不同接种程序的对比，但试验结果是复杂的。Zhang 等 [34] 的研究表明，以 2 周为间隔接种疫苗的受试者获得了更快的免疫反应，但以 4 周为间隔接种疫苗的受试者获得了更强的免疫反应。但 Che 等 [28] 在以 2 周为间隔接种疫苗的受试者中检测到了更强的免疫反应，Xia 等 [21] 也发现以 2 周为间隔接种疫苗的受试者不良反应发生率低于以 4 周为间隔接种疫苗的受试者。在 6 项比较了疫苗的单剂量与双剂量接种的研究中，4 项研究显示疫苗双剂量接种比单剂量接种产生更强的免疫反应 [19,31,33,35]。

2.4.5 疫苗类型差异的影响　Polack 等 [20] 报道的 RNA 疫苗（BNT162b2）和 Voysey 等 [19] 报道的腺病毒重组载体疫苗（ChAdOx1 nCoV-19）受试者人数超过 10 000 人，都采用相对危险度计算有效率，显示前者有效率为 95%[20]，后者有效率为 70.4%[19]。其他临床试验的设计存在差异，受试者规模较小，结局指标也有所不同，其有效率尚无法比较。

表 4　疫苗的有效性和安全性

研究	主要有效性指标	总不良反应发生率 [%(*n*/*N*)]	严重不良反应发生率 [%(*n*/*N*)]	最常见的不良反应	
				局部	系统性
Voysey 2021[19]	有效率 70.4%*	不详	0.15(84/55 048)	压痛	疲劳
Polack 2020[20]	有效率 95%**	27.0#	不详	疼痛	疲劳
Xia 2020[21]	14 d 血清转化率：标准剂量组 97.6%；14 d GMT：标准剂量组 121	15.0(36/240)	0(0/240)	疼痛	发热
Pu 2020[22]	28 d 血清转化率：低、中、高剂量组分别为 80%、96%、92%；28 d GMT：低、中、高剂量组分别为 10.6、15.4、19.6	25.7(37/144)	0(0/144)	疼痛	疲劳
Xia 2021[27]	28 d 血清转化率：低、中、高剂量组均为 100%；28 d GMT：低、中、高剂量组分别为 13.4、18.9、23.7	29.2(42/144)	0(0/144)	疼痛	发热
Che 2020[28]	28 d 血清转化率：中剂量组 92%，高剂量组 96%；28 d GMT：中剂量组 19，高剂量组 21	24.5(146/595)	0(0/595)	疼痛	疲劳
Ella 2020[29]	28 d 血清转化率：低剂量组 87.9%，高剂量组 91.9%；28 d GMT：低剂量组 61.7，高剂量组 66.4	不详	不详	疼痛	疲劳
Keech 2020[30]	35 d GMT：比恢复期血清高 4~6 倍	不详	1.96(2/102)	压痛	关节痛
Mulligan 2020[31]	28 d GMT：低剂量组 168，中剂量组 267	52.8(19/36)	5.6(2/36)	疼痛	疲劳
Richmond 2020[32]	36 d 血清转化率：低、中、高剂量组分别为 95%、100%、100%	34.7(41/118)	1.69(2/118)	疼痛	头痛
Walsh 2020[33]	BNT162b1 疫苗 28 d GMT：低、中、高剂量组分别为 168、167、267；BNT162b2 疫苗 28 d GMT：低、中、高剂量组分别为 157、263、361	39.1(61/156)	4.49(7/156)	疼痛	疲劳
Zhang 2021[34]	28 d 血清转化率：低剂量组 25%，高剂量组 83%；28 d GMT：低剂量组 5.4，高剂量组 15.2	26.6(151/568)	1.04(1/96)	疼痛	疲劳
Zhu 2020[35]	28 d 血清转化率：低剂量和标准剂量组分别为 59%、47%；28 d GMT：低剂量组 18.3，标准剂量组 19.5	73.0(279/382)	6.5(25/382)	疼痛	疲劳

注：GMT 为中和抗体几何平均滴度；* 有效率由校正后的相对危险度计算；** 有效率 =100 ×（1–IRR），IRR 为疫苗组每 1 000 人年随访中确诊的 COVID-19 病例数与安慰剂组相应病例的比率；# 原文献仅给出不良反应率，未给出具体人数。

3 讨论

本系统评价得出以下结论：（1）除了 Zhu 等[35]报道的疫苗外，所有候选疫苗都具有良好的免疫原性和安全性。接种后 28 d 内，受试者血清 GMT 显著增加，血清转化率大多大于 80%，大部分疫苗的不良反应率低于 30%，且以轻到中度为主，24 h 内缓解。（2）接种后产生的效价和不良反应率与剂量呈正相关，因此，大部分临床试验进入 III 期阶段后，选择了中等剂量作为标准剂量，这可能是对有效性和安全性综合考虑的结果。（3）相同条件下，疫苗对 60 岁以上的老年人的免疫原性较差，但不良反应率也偏低，一种可能的解释是这与人体的免疫衰老有关。老年人群对疫苗的耐受性需要继续研究。此外，目前尚没有针对未成年人的临床试验结果发表。（4）大部分疫苗研究都推荐双剂量接种，但接种间隔时间需进一步研究。

然而，本系统评价有一定的局限性：（1）缺乏疫苗的长期有效性和安全性的证据。由于疫苗研发的急迫性，大部分试验只随访到了接种后 28 d，中和性抗体能否长期维持，接种疫苗后是否有迟发的不良反应，仍需要更长时间的随访。（2）为了纳入更多最新证据，本系统评价也将预印本文献包含在内，这些文献没有经过同行评议，且其中一些数据无法获取。（3）本系统评价只纳入了随机、双盲、对照试验，而观察性研究、回顾性病例分析及早期的动物试验均被排除在外。如 Anderson 等[36]实施的一项开放标签试验发现 mRNA-1273 疫苗在老年人群体具有较好的安全性，Logunov 等[37]在非随机临床试验中报道了两种腺病毒重组载体疫苗制剂（rAd26-S 和 rAd5-S）在 18~60 岁健康人群具有较好的安全性和免疫原性。（4）各项临床试验的设计存在差异，导致无法对不同类型疫苗的优劣进行比较，如 Voysey 等[19]和 Polack 等[20]采用相对危险度计算有效率，Keech 等[30]未做病毒中和试验，其余 10 项研究虽然均完成了病毒中和试验，但试验设计方案差异较大[21-22,27-29,31-35]。（5）本系统评价只检索了中英文文献，以日文、法文等其他语言发表的文献被排除在外。

综上所述，本系统评价总结了 COVID-19 疫苗相关的临床试验结果，表明大部分疫苗都具有较好的安全性和有效性。这让我们有理由相信，随着 COVID-19 疫苗的广泛接种，有望控制、终结 COVID-19 的全球大流行。

利益冲突声明：所有作者均声明不存在利益冲突。

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