European Review for Medical and Pharmacological Sciences 2024; 28: 2584-2592

Evaluation of vaccine effectiveness of mRNA COVID-19 vaccines in children: a systematic review and meta-analysis

Y.-H. HU, Y. DING, L.-W. LI, J. CHENG, Y.-H. CAI

Department of Pediatrics, Chongqing University Jiangjin Hospital, Chongqing, China

Yanghong Hu and Yang Ding are equal contributors and co-first authors

Abstract. – OBJECTIVE: To evaluate the vaccine effectiveness (VE) of mRNA COVID-19 vaccines in children using a meta-analysis approach.

MATERIALS AND METHODS: Relevant studies on the use of mRNA COVID-19 vaccines in children were identified through computerized searches. VE-related indicators were extracted, and data analysis was performed using the R software with the meta-package.

RESULTS: This study included a total of 12 relevant articles involving 9,963,732 participants from multiple centers in different countries, including the United States, Canada, Singapore, Israel, South Korea, and Qatar. The administered vaccine types included BNT162b2 and mRNA-1273. Participants were categorized into partially immunized (one dose of vaccine) and fully immunized (two doses of vaccine). Four articles reported VE after one dose of vaccine, while 12 reported VE after two doses. Heterogeneity analysis indicated significant heterogeneity among the studies, warranting the use of a random-effects model for analysis. Meta-analysis results revealed that the VE of partial immunization ranged from 16.61 (95% CI: 6.32-25.77) to 34.30 (95% CI: 24.21-43.04), with a pooled VE of 22.80 (95% CI: 15.68-29.32). The VE after full immunization ranged from 16.14 (95% CI: 14.42-17.83) to 90.47 (95% CI: 67.42-97.21), with a pooled VE of 56.17 (95% CI: 41.12-67.37). Meta-regression analysis showed no statistically significant correlation between VE and time ($p>0.05$).

CONCLUSIONS: Both partial and full immunization of the BNT162b2 mRNA vaccine provide benefits in reducing infection rates. VE varies over time and is closely associated with viral mutations and waning immunity. The specific mechanisms require further investigation.

Key Words:
COVID-19, Vaccine, mRNA, Vaccine effectiveness.

Introduction

The Coronavirus Disease 2019 (COVID-19) has been officially declared as an international public health emergency by the World Health Organization (WHO) due to its rapid and extensive dissemination across the world[1]. The COVID-19 pandemic has accounted for substantial morbidity and mortality. Infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) can cause various severe complications, including Multisystem Inflammatory Syndrome in Children (MIS-C)[2]. Due to social interaction, school-aged children (5 to 11 years old) constituted a significant proportion of COVID-19 cases and substantially contributed to the dissemination of SARS-CoV-2[3,4], resulting in significantly compromised physical and psychological health of the children. Thus, vaccination is of great importance[5].

Vaccination is the cornerstone for preventing infections and reducing mortality rates. The administration of vaccines has eradicated the impact of contagious diseases such as smallpox, measles, and polio on public health. Safe and effective administration of COVID-19 mRNA vaccines offered benefits in disease prevention in children and contributed to their return to normal life and school. COVID-19 mRNA vaccines have shown[6,7] safety, immunogenicity, and effectiveness against SARS-CoV-2 in adults, as well as in adolescents (aged 12-18 years) and children (aged 5-11 years). They have received authorization from the U.S. Food and Drug Administration and, by the end of 2021, from the European Medicines Agency for their use in children aged 5 to 11. Early data4 on the COVID-19 pandemic indicated a comparatively lower risk of illness in children. Coupled with vaccine safety apprehensions, this has led to limited vaccination of children globally, especially those under 11 years old, resulting in a slow implementation of vaccination efforts[8]. As of the end of 2021 and before the Omicron surge, about 50-70% of children worldwide remained vulnerable to COVID-19, emphasizing the necessity for improved vaccines and expanded vaccination coverage among children[9].

Corresponding Author: Yihong Cai; e-mail: nany1122@163.com

Children experience milder symptoms after contracting COVID-19 than adults, and the injection of vaccine in children has been a subject of debate[10]. Furthermore, evidence[11] suggests that since the transition from the Delta to the Omicron variant of the COVID-19 virus, the likelihood of severe COVID-19 in children aged 6 to 11 has significantly decreased (OR=0.47, 95% CI: 0.33-0.66). While the Omicron variant is known for its increased transmissibility, instances of MIS-C have been infrequently documented[12].

The recommended metric for determining vaccine efficacy is vaccine effectiveness (VE)[13]. Therefore, given the lower risk of severe illness in children after contracting COVID-19, a careful evaluation of the VE of COVID-19 vaccination is warranted. This study employs a meta-analysis approach to evaluate the VE of mRNA COVID-19 vaccines in children.

Materials and Methods

Search Strategy

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. We conducted a systematic search of the PubMed, Medline, and Embase databases, as well as the China National Knowledge Infrastructure (CNKI), VIP, and Wanfang databases. The search was conducted from the inception of the databases up until April 25, 2022. English search terms included: "vaccine," "vaccination," "mRNA vaccines," "COVID-19," and "SARS-CoV-2." Chinese search terms included: "新冠肺炎" (COVID-19), "新冠病毒感染" (COVID-19 virus infection), and "mRNA疫苗" (mRNA vaccines).

Inclusion and Exclusion Criteria

Inclusion criteria: (1) Study participants aged 5-11 years with no underlying comorbidities; (2) Intervention involved administration of COVID-19 mRNA vaccines, regardless of the vaccine type; (3) Study design was randomized controlled clinical trials; (4) Outcome measures included basic demographic information, types and doses of vaccines used, gender, age, time interval from vaccination to follow-up, and SARS-CoV-2 infection status.

Exclusion criteria: (1) Basic experiments; (2) Studies focused on children under 12 years old or adults (≥18 years old); (3) Case reports or case series reports; (4) Study participants with underlying comorbidities; (5) Patients in the study who were already infected with SARS-CoV-2 before vaccination; (6) Inappropriate statistical methods; (7) Incomplete data; (8) Duplicate publications.

Literature Screening

The retrieved literature was imported into Endnote software. Two review authors independently screened titles and abstracts to identify relevant studies. Full texts of potentially eligible articles were read to determine their eligibility. Any discrepancies between the two reviewers were resolved through discussion and adjudicated by a third reviewer. Full reports were retrieved for every record deemed potentially eligible. Two review authors independently screened these full-text articles to determine the studies to be included in the review. In case of disagreements, consensus was reached through discussion with a third reviewer. Reasons for excluding full-text reports were recorded, and duplicate records were removed.

Data Collection

A standardized data extraction form was developed using Excel software to collect data from the included literature. The collected data included publication information, basic information about study participants, types and doses of vaccines used, gender, age, time interval from vaccination to follow-up, and SARS-CoV-2 infection status. Any discrepancies in data extraction were resolved through discussion or by a third reviewer.

Statistical Analysis

R software (MathSoft, version 4.0.3, available at: https://www.r-project.org) was used for data analysis. Heterogeneity among included studies was measured using I^2, and the Cochran Q test was used to test heterogeneity. An I^2 of 0% indicated no observed heterogeneity, with increasing values indicating increasing heterogeneity. In this study, I^2>50% indicated significant heterogeneity among the studies, requiring subgroup analysis or the use of a random-effects model; I^2≤50% indicated no significant heterogeneity among the studies, and a fixed-effects model was used for analysis. A significance level of p<0.05 was set for determining statistical significance. A funnel plot was used for visual assessment of publication bias. The primary outcome measure assessed in this study was VE, calculated by the formula: VE=(Infection rate in the placebo group during a certain observation period - Infection rate in the vaccine group) / Infection rate in the placebo group.

Results

Literature Selection Results

A total of 647 articles were identified through database searches and additional sources. After removing duplicates, 326 articles remained. Following the inclusion and exclusion criteria, and after reviewing abstracts and full texts to exclude irrelevant studies, a total of 12 articles[7,14-24] were included for meta-analysis. The flowchart of literature selection is presented in Figure 1. Among the included studies, a total of 9,963,732 participants from multiple centers were involved, spanning countries such as the United States, Canada, Singapore, Israel, South Korea, and Qatar. The administered vaccine types included BNT162b2 and mRNA-1273. Basic information about the included studies is provided in Table I.

Partial Immunization VE Analysis

Participants were categorized into partially immunized (receiving one vaccine dose) and fully immunized groups (receiving two vaccine doses). Four studies[16,17,19,21] reported the effectiveness of partial immunization. Heterogeneity analysis indicated significant heterogeneity among the studies[16,17,19,21] (I^2=80%, p<0.01), resulting in the use of a random-effects model for analysis. The results revealed that the highest VE for partial immunization was 16.61 (95% CI: 6,3225.77), with a peak of 34.30 (95% CI: 24,2143.04). The pooled VE was 22.80 (95% CI: 15.68-29.32). The forest plot for VE in partial immunization is illustrated in Figure 2. An assessment of publication bias using a funnel plot demonstrated significant asymmetry, as shown in Figure 3.

Full Immunization VE Analysis

Among the 12 studies[7,14-24] that reported the effectiveness of full immunization, a significant heterogeneity was observed across the studies[7,14-24] (I^2=100%, p<0.01). The results of the meta-analysis using a random-effects model indicated that the highest VE for full immunization was 16.14 (95% CI: 14.42-17.83), with the maximum reaching 90.47 (95% CI: 67.42-97.21). The pooled VE was calculated to be 56.17 (95% CI: 41.12-67.37). The forest plot depicting the VE for full immunization is shown in Figure 4. A funnel plot that was used to assess publication bias exhibited significant asymmetry, as illustrated in Figure 5.

The Influence of Time After Full Immunization on VE

To further explore the impact of time on VE, a meta-regression analysis was conducted based on the median follow-up time after achieving full immunization.

Table I. Basic information from the included literature.

Author	Year	Country	Vaccine	Study Type	n	Age	Gender (Male/ Female)	Outcome
Walter et al[7]	2021	US	BNT162b2	RCT	2,268	8.2±1.94	1,182/1,086	2 doses
Creech et al[14]	2022	US and Canada	mRNA-1273	RCT	4,002	8.5±1.7	2,035/1,967	2 doses
Klein et al[15]	2022	US	BNT162b2	Real-world	9,181	-	-	2 doses
Tan et al[16]	2022	Singapore	BNT162b2	Real-world	255,936	-	-	1 dose and 2 doses
Cohen-Stavi et al[17]	2022	Israel	BNT162b2	Matched Case-control	189,456	-	97,290/ 92,116	1 dose and 2 doses
Glatman-Freedman et al[18]	2023	Israel	BNT162b2	Matched Case-control	157,082	-	39,366/ 39,375	2 doses
Oliveira et al[19]	2023	China	BNT162b2 and CoronaVac	Case-control	6,947	7.5±1.9	3,734/3,213	1 dose and 2 doses
Jang et al[20]	2023	South Korea	BNT162b2	Real-world	3,062,281	-	1,570,185/ 1,492,096	2 doses
Sacco et al[21]	2022	Italy	BNT162b2	Retrospective analysis	2,965,918	-	1,524,752/ 1,441,166	1 dose and 2 doses
Price et al[22]	2022	US	BNT162b2	Case-control	537	-	301/236	2 doses
Mattiuzzi and Lippi[23]	2022	Italy	BNT162b2	Real-world	3,196,066	-	-	2 doses
Chemaitelly et al[24]	2022	Qatar	BNT162b2	Real-world	113,758	57,976	55,782	2 doses

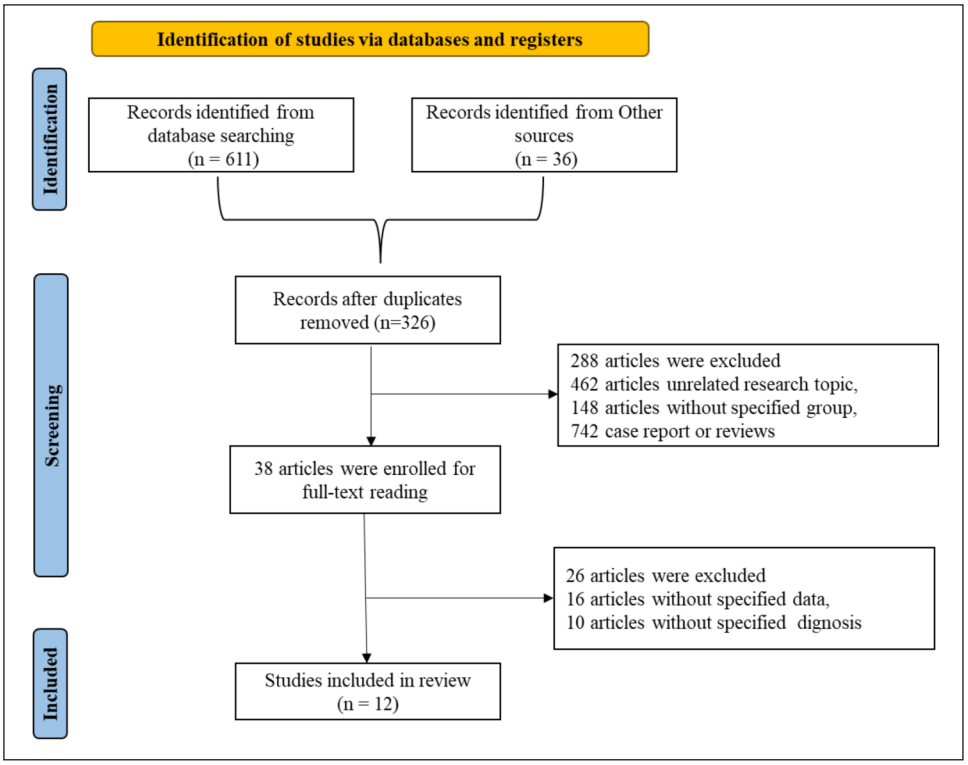

Figure 1. Flowchart diagram.

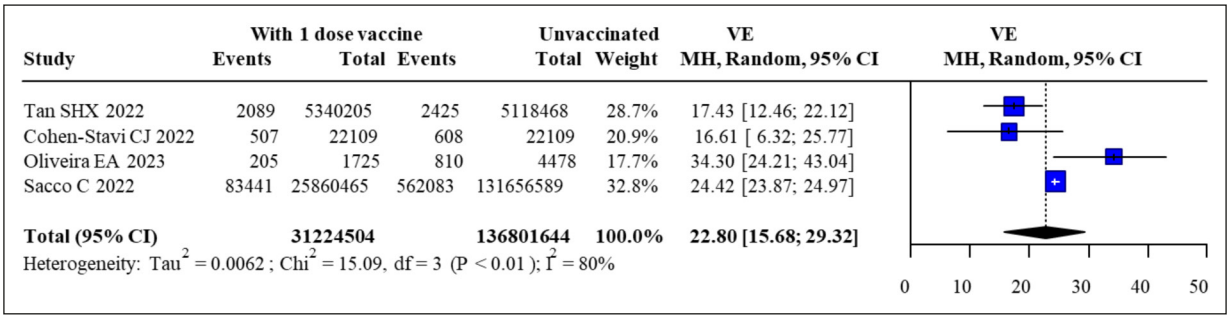

Figure 2. VE forest of partial immunization.

A bubble plot was used to illustrate the relationship between vaccine administration, infection, and post-immunization time. The size of the bubbles represents the variance of the effect size; the larger the circle, the smaller the variance of the effect size in the study, indicating higher precision and greater weight. Notable, no statistically significant correlation between VE and time was observed (p>0.05). The meta-regression bubble plot is presented in Figure 6.

Discussion

On March 11, 2020, the WHO declared a global pandemic of COVID-19, severely affecting the physical and mental health of individuals. Immunization stands as a primary means to control severe infectious diseases. COVID-19 vaccination began in December 2020, initially targeting healthcare workers and vulnerable populations, later extending to healthy individuals aged 12 and above[25]. In the early stages of the global pandemic, the prevalence and severity of COVID-19 in children were remarkably low, possibly due to the higher occurrence of asymptomatic or mild cases[26]. In November 2021, the U.S. FDA granted emergency use authorization for the BNT162b2 mRNA vaccine for preventing COVID-19 in children aged 5 to 11[27].

This study included a total of 12[7,14-24] research articles involving 9,963,732 participants from

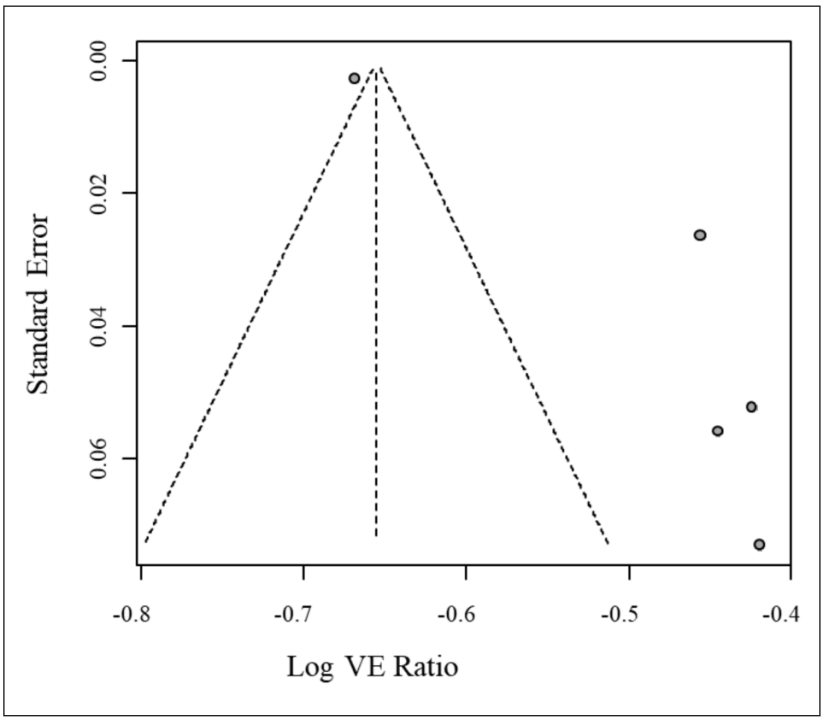

Figure 3. Funnel plot of partial immunization.

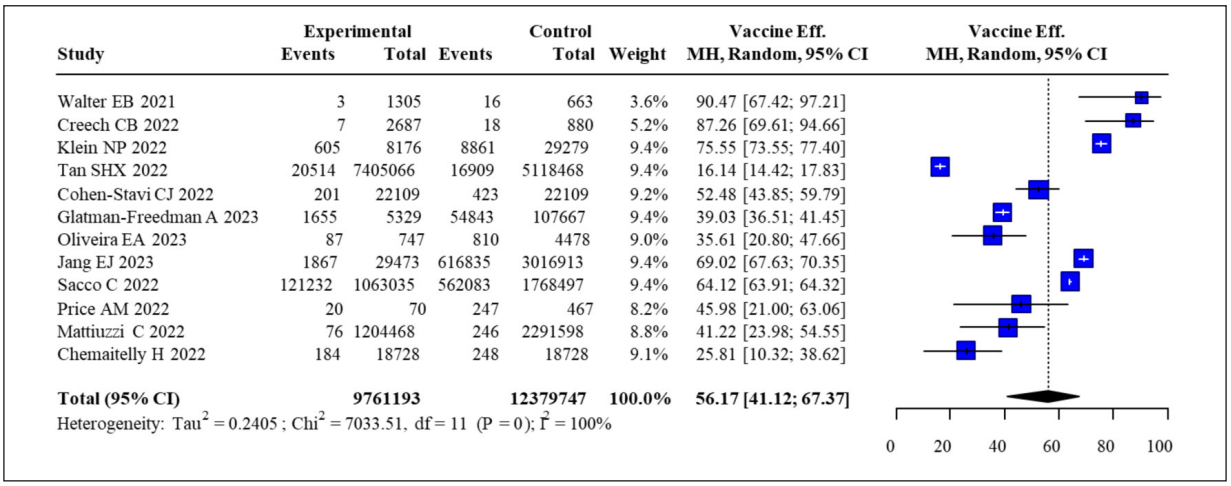

Figure 4. VE forest of full immunization.

multiple centers in different countries. The vaccines administered in these studies were BNT162b2 and mRNA-1273. The VE for individuals was 22.80% (95% CI: 15,6829.32) for partial immunization and 56.17% (95% CI: 41,1267.37) for full immunization. VE after mRNA vaccination varies significantly among different age groups. A systematic review and meta-analysis[28] providing information for the Advisory Committee for Immunization Practices (ACIP) policy discussions found that compared to unvaccinated adults, the BNT162b2 vaccine showed a high protective effect against symptomatic laboratory-confirmed COVID-19 (VE: 92.4%), COVID-19 hospitalization (VE: 94.3%), COVID-19 mortality (VE: 96.1%), and asymptomatic SARS-CoV-2 infection (VE: 88.1%), forming the evidential basis for the widespread use of BNT162b2. For adolescents, a meta-analysis by Katoto et al[29], which included 15 studies, analyzed the VE of mRNA vaccines for individuals aged 12 to 17. It confirmed that BNT162b2 can protect fully immunized teenagers, reducing the risk of COVID-19 infection by 82.7% (95% CI: 78.37-87.31%). In clinical practice,

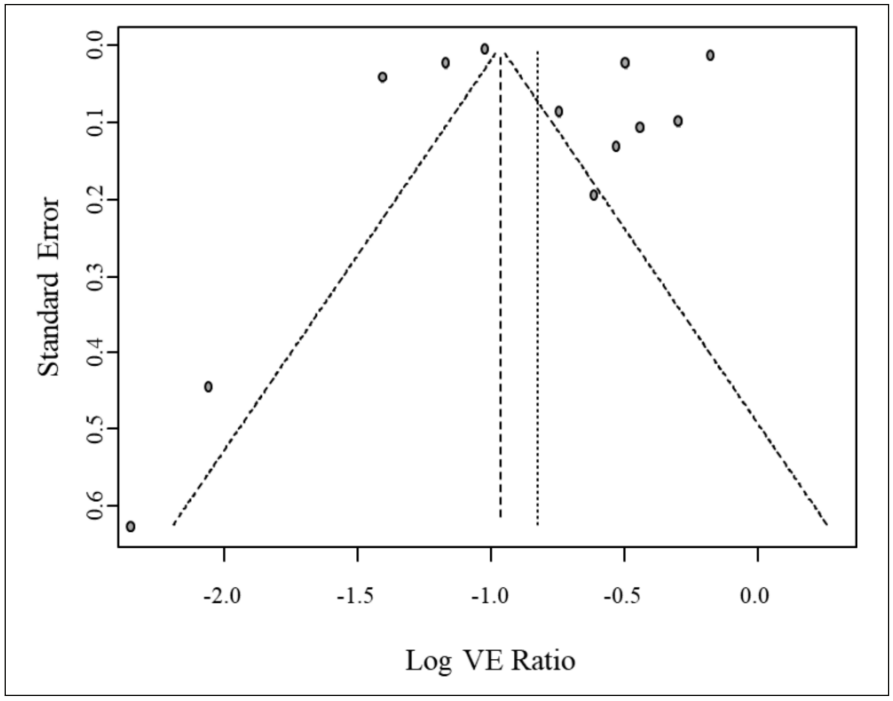

Figure 5. Funnel plot of full immunization.

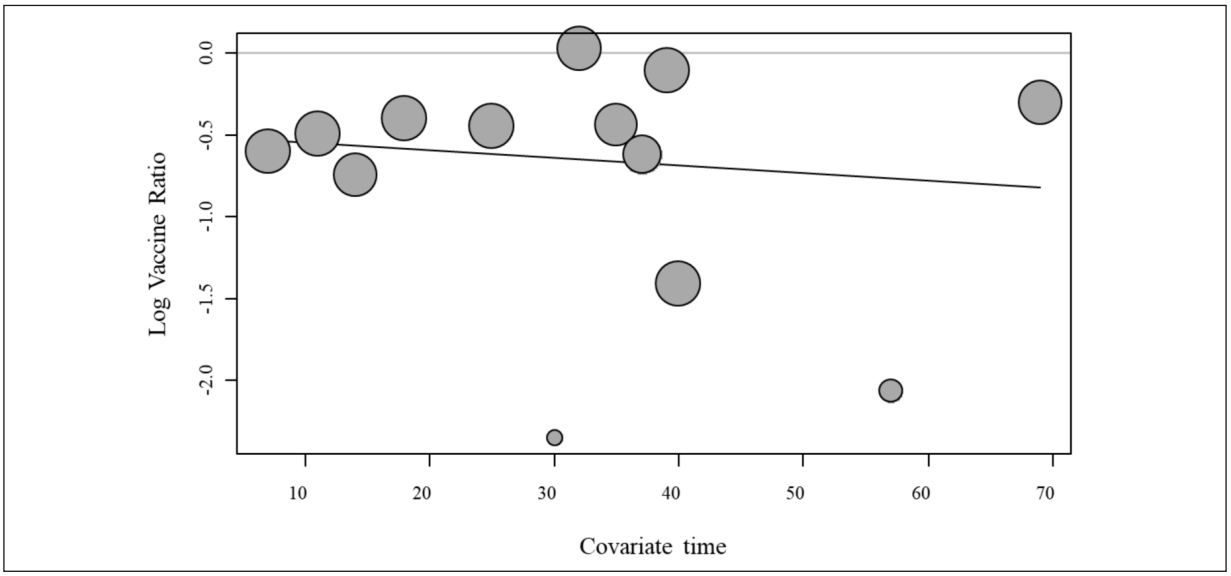

Figure 6. Meta-regression bubble chart.

BNT162b2 has been remarkably effective in reducing COVID-19 hospitalization and severe risks among adolescents aged 12 to 18. However, data on the effectiveness of the vaccine for children aged 5 to 11 is scarce. An early meta-analysis[30] of a study targeting the Omicron variant indicated that mRNA vaccines provided a moderate level of protection in children aged 5 to 11, with a VE of 41.6% (95% CI: 28.1-52.6%), thus establishing an evidential basis for COVID-19 vaccination in this age group. Unlike this study, which did not limit the type of infection, our research focused on individuals with no prior infection, leading to higher results. A typical phenomenon observed[31] in most vaccines is a decline in effectiveness over time due to waning immunity. There are reports in the literature[32] that state that an increasing number of patients with newly developed autoimmune inflammatory rheumatism (AIRD) after receiving the COVID-19 vaccine have developed AIRD-related

symptoms after three doses of vaccination. Rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, psoriatic arthritis, ankylosing spondylitis, systemic sclerosis, mixed connective tissue disease, and eosinophilic granulomatosis are, respectively, polyangitis and inflammatory myositis. After receiving the COVID-19 vaccine, autoimmune or inflammatory rheumatism may occur. Waning immunity and viral mutations may have repercussions on VE over time. The results of a Phase II/III RCT study[33] suggested reduced effectiveness against symptomatic laboratory-confirmed COVID-19 after more than four months of vaccination. In the current study, we utilized meta-regression to analyze the impact of post-vaccination time on VE and found no statistically significant correlation between post-vaccination time and VE, possibly related to significant heterogeneity among studies.

This study exhibits significant heterogeneity and publication bias, primarily due to several factors. First, there are substantial regional and temporal variations in COVID-19 infections, resulting in markedly different outcomes in different times and areas. Second, there is a noticeable disparity in follow-up duration. In this study, the shortest follow-up period was 7 days after full vaccination, while the longest was 6 months. Because VE is closely associated with time, this leads to significant heterogeneity among different studies.

Conclusions

Both partial and full immunization of the BNT162b2 mRNA vaccine provide benefits in reducing infection rates. Vaccine VE varies over time and is closely associated with viral mutations and waning immunity. The specific mechanisms require further investigation.

Data Availability

All data generated or analyzed during this study are included in this published article.

Acknowledgments

We thank some students from Chongqing University Jiangjin Hospital for their kind support.

Authors' Contributions

Yihong Cai conceived study design and content concept; Yanghong Hu and Yang Ding performed the data collection, extraction and analyzed the data; Linwei Li and Jun Cheng were responsible for literature search; Yihong Cai interpreted and reviewed the data and drafts.

Funding

The study was funded by research projects of the Guangxi Zhuang Autonomous Region Health Commission (Grant No. Z20211292).

Conflict of Interest

The authors declare that they have no competing interests.

Ethics Approval and Informed Consent

Not applicable.

ORCID ID

Yanghong Hu: 0009-0009-3079-4124
Yang Ding: 0009-0009-3026-1272
Linwei Li: 0009-0000-1808-7130
Jun Cheng: 0000-0002-1849-9554
Yihong Cai: 0009-0003-5871-767X.

References

1) Maxmen A. Why did the world's pandemic warning system fail when COVID hit? Nature 2021; 589: 499-500.
2) Guimarães D, Pissarra R, Reis-Melo A, Guimarães H. Multisystem inflammatory syndrome in children (MISC): A systematic review. Int J Clin Pract 2021; 75: e14450.
3) Rumain B, Schneiderman M, Geliebter A. Prevalence of COVID-19 in adolescents and youth compared with older adults in states experiencing surges. PLoS One 2021; 16: e0242587.
4) Szablewski CM, Chang KT, Brown MM, Chu VT, Yousaf AR, Anyalechi N, Aryee PA, Kirking HL, Lumsden M, Mayweather E, McDaniel CJ, Montierth R, Mohammed A, Schwartz NG, Shah JA, Tate JE, Dirlikov E, Drenzek C, Lanzieri TM, Stewart RJ. SARS-CoV-2 Transmission and Infection Among Attendees of an Overnight Camp - Georgia, June 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 1023-1025.
5) Marchetti F, Tamburlini G. Other good reasons for covid-19 vaccination in pre-adolescent and adolescent populations. BMJ 2021; 374: n2052.
6) Frenck RW, Jr., Klein NP, Kitchin N, Gurtman A, Absalon J, Lockhart S, Perez JL, Walter EB, Senders S, Bailey R, Swanson KA, Ma H, Xu X, Koury K, Kalina WV, Cooper D, Jennings T, Brandon DM, Thomas SJ, Türeci Ö, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC. Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. N Engl J Med 2021; 385: 239-250.

7) Walter EB, Talaat KR, Sabharwal C, Gurtman A, Lockhart S, Paulsen GC, Barnett ED, Muñoz FM, Maldonado Y, Pahud BA, Domachowske JB, Simões EAF, Sarwar UN, Kitchin N, Cunliffe L, Rojo P, Kuchar E, Rämet M, Munjal I, Perez JL, Frenck RW, Jr., Lagkadinou E, Swanson KA, Ma H, Xu X, Koury K, Mather S, Belanger TJ, Cooper D, Türeci Ö, Dormitzer PR, Şahin U, Jansen KU, Gruber WC. Evaluation of the BNT162b2 Covid-19 Vaccine in Children 5 to 11 Years of Age. N Engl J Med 2022; 386: 35-46.

8) Nathanielsz J, Toh ZQ, Do LAH, Mulholland K, Licciardi PV. SARS-CoV-2 infection in children and implications for vaccination. Pediatr Res 2023; 93: 1177-1187.

9) Naeimi R, Sepidarkish M, Mollalo A, Parsa H, Mahjour S, Safarpour F, Almukhtar M, Mechaal A, Chemaitelly H, Sartip B, Marhoommirzabak E, Ardekani A, Hotez PJ, Gasser RB, Rostami A. SARS-CoV-2 seroprevalence in children worldwide: A systematic review and meta-analysis. EClinicalMedicine 2023; 56: 101786.

10) Mehta NS, Mytton OT, Mullins EWS, Fowler TA, Falconer CL, Murphy OB, Langenberg C, Jayatunga WJP, Eddy DH, Nguyen-Van-Tam JS. SARS-CoV-2 (COVID-19): What Do We Know About Children? A Systematic Review. Clin Infect Dis 2020; 71: 2469-2479.

11) Butt AA, Dargham SR, Loka S, Shaik RM, Chemaitelly H, Tang P, Hasan MR, Coyle PV, Yassine HM, Al-Khatib HA, Smatti MK, Kaleeckal AH, Latif AN, Zaqout A, Almaslamani MA, Al Khal A, Bertollini R, Abou-Samra AB, Abu-Raddad LJ. Coronavirus Disease 2019 Disease Severity in Children Infected With the Omicron Variant. Clin Infect Dis 2022; 75: e361-e367.

12) Sperotto F, Gutiérrez-Sacristán A, Makwana S, Li X, Rofeberg VN, Cai T, Bourgeois FT, Omenn GS, Hanauer DA, Sáez C, Bonzel CL, Bucholz E, Dionne A, Elias MD, García-Barrio N, González TG, Issitt RW, Kernan KF, Laird-Gion J, Maidlow SE, Mandl KD, Ahooyi TM, Moraleda C, Morris M, Moshal KL, Pedrera-Jiménez M, Shah MA, South AM, Spiridou A, Taylor DM, Verdy G, Visweswaran S, Wang X, Xia Z, Zachariasse JM, Newburger JW, Avillach P. Clinical phenotypes and outcomes in children with multisystem inflammatory syndrome across SARS-CoV-2 variant eras: a multinational study from the 4CE consortium. EClinicalMedicine 2023; 64: 102212.

13) Sarkar A, Omar S, Alshareef A, Fanous K, Sarker S, Alroobi H, Zamir F, Yousef M, Zakaria D. The relative prevalence of the Omicron variant within SARS-CoV-2 infected cohorts in different countries: A systematic review. Hum Vaccin Immunother 2023; 19: 2212568.

14) Creech CB, Anderson E, Berthaud V, Yildirim I, Atz AM, Melendez Baez I, Finkelstein D, Pickrell P, Kirstein J, Yut C, Blair R, Clifford RA, Dunn M, Campbell JD, Montefiori DC, Tomassini JE, Zhao X, Deng W, Zhou H, Ramirez Schrempp D, Hautzinger K, Girard B, Slobod K, McPhee R, Pajon R, Das R, Miller JM, Schnyder Ghamloush S. Evaluation of mRNA-1273 Covid-19 Vaccine in Children 6 to 11 Years of Age. N Engl J Med 2022; 386: 2011-2023.

15) Klein NP, Stockwell MS, Demarco M, Gaglani M, Kharbanda AB, Irving SA, Rao S, Grannis SJ, Dascomb K, Murthy K, Rowley EA, Dalton AF, DeSilva MB, Dixon BE, Natarajan K, Stenehjem E, Naleway AL, Lewis N, Ong TC, Patel P, Konatham D, Embi PJ, Reese SE, Han J, Grisel N, Goddard K, Barron MA, Dickerson M, Liao IC, Fadel WF, Yang DH, Arndorfer J, Fireman B, Griggs EP, Valvi NR, Hallowell C, Zerbo O, Reynolds S, Ferdinands J, Wondimu MH, Williams J, Bozio CH, Link-Gelles R, Azziz-Baumgartner E, Schrag SJ, Thompson MG, Verani JR. Effectiveness of COVID-19 Pfizer-BioNTech BNT162b2 mRNA Vaccination in Preventing COVID-19-Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Nonimmunocompromised Children and Adolescents Aged 5-17 Years - VISION Network, 10 States, April 2021-January 2022. MMWR Morb Mortal Wkly Rep 2022; 71: 352-358.

16) [Tan SHX, Cook AR, Heng D, Ong B, Lye DC, Tan KB. Effectiveness of BNT162b2 Vaccine against Omicron in Children 5 to 11 Years of Age. N Engl J Med 2022; 387: 525-532.

17) [Cohen-Stavi CJ, Magen O, Barda N, Yaron S, Peretz A, Netzer D, Giaquinto C, Judd A, Leibovici L, Hernán MA, Lipsitch M, Reis BY, Balicer RD, Dagan N. BNT162b2 Vaccine Effectiveness against Omicron in Children 5 to 11 Years of Age. N Engl J Med 2022; 387: 227-236.

18) Glatman-Freedman A, Hershkovitz Y, Dichtiar R, Rosenberg A, Keinan-Boker L, Bromberg M. Effectiveness of BNT162b2 Vaccine against Omicron Variant Infection among Children 5-11 Years of Age, Israel. Emerg Infect Dis 2023; 29: 771-777.

19) Oliveira EA, Oliveira MCL, Silva A, Colosimo EA, Mak RH, Vasconcelos MA, Silva LR, Martelli DB, Pinhati CC, Martelli-Júnior H. Effectiveness of BNT162b2 and CoronaVac vaccines against omicron in children aged 5 to 11 years. World J Pediatr 2023; 19: 949-960.

20) Jang EJ, Choe YJ, Kim RK, Park YJ. BNT162b2 Vaccine Effectiveness Against the SARS-CoV-2 Omicron Variant in Children Aged 5 to 11 Years. JAMA Pediatr 2023; 177: 319-320.

21) Sacco C, Del Manso M, Mateo-Urdiales A, Rota MC, Petrone D, Riccardo F, Bella A, Siddu A, Battilomo S, Proietti V, Popoli P, Menniti Ippolito F, Palamara AT, Brusaferro S, Rezza G, Pezzotti P, Fabiani M. Effectiveness of BNT162b2 vaccine against SARS-CoV-2 infection and severe COVID-19 in children aged 5-11 years in Italy: a retrospective analysis of January-April, 2022. Lancet 2022; 400: 97-103.

22) Price AM, Olson SM, Newhams MM, Halasa NB, Boom JA, Sahni LC, Pannaraj PS, Irby K, Bline KE, Maddux AB, Nofziger RA, Cameron MA, Walker TC, Schwartz SP, Mack EH, Smallcomb L, Schuster JE, Hobbs CV, Kamidani S, Tarquinio KM,

Bradford TT, Levy ER, Chiotos K, Bhumbra SS, Cvijanovich NZ, Heidemann SM, Cullimore ML, Gertz SJ, Coates BM, Staat MA, Zinter MS, Kong M, Chatani BM, Hume JR, Typpo KV, Maamari M, Flori HR, Tenforde MW, Zambrano LD, Campbell AP, Patel MM, Randolph AG. BNT162b2 Protection against the Omicron Variant in Children and Adolescents. N Engl J Med 2022; 386: 1899-1909.

23) Mattiuzzi C, Lippi G. Real-world effectiveness of COVID-19 vaccination among children in Italy. Int J Infect Dis 2022; 122: 70-71.

24) Chemaitelly H, AlMukdad S, Ayoub HH, Altarawneh HN, Coyle P, Tang P, Yassine HM, Al-Khatib HA, Smatti MK, Hasan MR, Al-Kanaani Z, Al-Kuwari E, Jeremijenko A, Kaleeckal AH, Latif AN, Shaik RM, Abdul-Rahim HF, Nasrallah GK, Al-Kuwari MG, Al-Romaihi HE, Butt AA, Al-Thani MH, Al-Khal A, Bertollini R, Abu-Raddad LJ. Covid-19 Vaccine Protection among Children and Adolescents in Qatar. N Engl J Med 2022; 387: 1865-1876.

25) Heifetz A. Accelerating COVID-19 Drug Discovery with High-Performance Computing. Methods Mol Biol 2024; 2716: 405-411.

26) Hon KLE, Leung AKC, Leung KKY, Wong AHC. Impact of "Long Covid" on Children: Global and Hong Kong Perspectives. Curr Pediatr Rev 2024; 20: 59-65.

27) Nantanee R, Jaru-Ampornpan P, Chantasrisawad N, Himananto O, Papakhee S, Sophonphan J, Tawan M, Jupimai T, Anugulruengkitt S, Puthanakit T. Immunogenicity of BNT162b2 in children 6 months to under 5 years of age with previous SARS-CoV-2 infection, in the era of Omicron predominance. Vaccine X 2023; 15: 100367.

28) Wallace M, Collins JP, Moline H, Plumb ID, Godfrey M, Morgan RL, Campos-Outcalt D, Oliver SE, Dooling K, Gargano JW. Effectiveness of Pfizer-BioNTech COVID-19 vaccine as evidence for policy action: A rapid systematic review and meta-analysis of non-randomized studies. PLoS One 2022; 17: e0278624.

29) Katoto PD, Tamuzi JL, Brand AS, Marangu DM, Byamungu LN, Wiysonge CS, Gray G. Effectiveness of COVID-19 Pfizer-BioNTech (BNT162b2) mRNA vaccination in adolescents aged 12-17 years: A systematic review and meta-analysis. Hum Vaccin Immunother 2023; 19: 2214495.

30) Piechotta V, Siemens W, Thielemann I, Toews M, Koch J, Vygen-Bonnet S, Kothari K, Grummich K, Braun C, Kapp P, Labonté V, Wichmann O, Meerpohl JJ, Harder T. Safety and effectiveness of vaccines against COVID-19 in children aged 5-11 years: a systematic review and meta-analysis. Lancet Child Adolesc Health 2023; 7: 379-391.

31) Feikin DR, Higdon MM, Abu-Raddad LJ, Andrews N, Araos R, Goldberg Y, Groome MJ, Huppert A, O'Brien KL, Smith PG, Wilder-Smith A, Zeger S, Deloria Knoll M, Patel MK. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. Lancet 2022; 399: 924-944.

32) Akkuzu G, Bes C, Özgür DS, Karaalioğlu B, Mutlu MY, Yıldırım F, Atagündüz P, Gündüz A, Soy M. Inflammatory rheumatic diseases developed after COVID-19 vaccination: presentation of a case series and review of the literature[J]. Eur Rev Med Pharmacol Sci 2023; 27: 2143-2151.

33) Adams K, Rhoads JP, Surie D, Gaglani M, Ginde AA, McNeal T, Talbot HK, Casey JD, Zepeski A, Shapiro NI, Gibbs KW, Files DC, Hager DN, Frosch AE, Exline MC, Mohamed A, Johnson NJ, Steingrub JS, Peltan ID, Brown SM, Martin ET, Lauring AS, Khan A, Busse LW, Duggal A, Wilson JG, Chang SY, Mallow C, Kwon JH, Chappell JD, Halasa N, Grijalva CG, Lindsell CJ, Lester SN, Thornburg NJ, Park S, McMorrow ML, Patel MM, Tenforde MW, Self WH. Vaccine effectiveness of primary series and booster doses against covid-19 associated hospital admissions in the United States: living test negative design study. BMJ 2022; 379: e072065.