

# Efficacy and effectiveness of inactivated vaccines against symptomatic COVID-19, severe COVID-19, and COVID-19 clinical outcomes in the general population: a systematic review and meta-analysis

Martin Law,<sup>a,h</sup> Sam S. H. Ho,<sup>a,h</sup> Gigi K. C. Tsang,<sup>a</sup> Clarissa M. Y. Ho,<sup>a</sup> Christine M. Kwan,<sup>a,b,c</sup> Vincent Ka Chun Yan,<sup>a</sup> Hei Hang Edmund Yiu,<sup>a</sup> Francisco Tsz Tsun Lai,<sup>a,b</sup> Ian Chi Kei Wong,<sup>a,b,d,e,\*\*</sup> and Esther Wai Yin Chan<sup>a,b,f,g,\*</sup>



<sup>a</sup>Li Ka Shing Faculty of Medicine, Department of Pharmacology and Pharmacy, Centre for Safe Medication Practice and Research, The University of Hong Kong, Hong Kong SAR, China

<sup>b</sup>Laboratory of Data Discovery for Health (D<sup>2</sup>4H), Hong Kong Science and Technology Park, Hong Kong SAR, China

<sup>c</sup>Sau Po Centre on Ageing, The University of Hong Kong, Hong Kong SAR, China

<sup>d</sup>Research Department of Practice and Policy, UCL School of Pharmacy, London, United Kingdom

<sup>e</sup>Aston Pharmacy School, Aston University, Birmingham, United Kingdom

<sup>f</sup>Department of Pharmacy, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China

<sup>g</sup>The University of Hong Kong Shenzhen Institute of Research and Innovation, Shenzhen, China

## Summary

**Background** Inactivated, whole-virion vaccines have been used extensively in the SARS-CoV-2 pandemic. Its efficacy and effectiveness across regions have not been systematically evaluated. Efficacy refers to how well a vaccine performs in a controlled environment. Effectiveness refers to how well it performs in real world settings.

**Methods** This systematic review and meta-analysis reviewed published, peer-reviewed evidence on all WHO-approved inactivated vaccines and evaluated their efficacy and effectiveness against SARS-CoV-2 infection, symptomatic infection, severe clinical outcomes, and severe COVID-19. We searched Pubmed (including MEDLINE), EMBASE (via OVID), Web of Science Core Collection, Web of Science Chinese Science Citation Database, and [Clinicaltrials.gov](https://www.clinicaltrials.gov).

**Findings** The final pool included 28 studies representing over 32 million individuals reporting efficacy or effectiveness estimates of complete vaccination using any approved inactivated vaccine between January 1, 2019 and June 27, 2022. Evidence was found for efficacy and effectiveness against symptomatic infection (OR 0.21, 95% CI 0.16–0.27,  $I^2 = 28\%$  and OR 0.32, 95% CI 0.16–0.64,  $I^2 = 98\%$ , respectively) and infection (OR 0.53, 95% CI 0.49–0.57,  $I^2 = 90\%$  and OR 0.31, 95% CI 0.24–0.41,  $I^2 = 0\%$ , respectively) for early SARS-CoV-2 variants of concern (VoCs) (Alpha, Delta), and for waning of vaccine effectiveness with more recent VoCs (Gamma, Omicron). Effectiveness remained robust against COVID-related ICU admission (OR 0.21, 95% CI 0.04–1.08,  $I^2 = 99\%$ ) and death (OR 0.08, 95% CI 0.00–2.02,  $I^2 = 96\%$ ), although effectiveness estimates against hospitalization (OR 0.44, 95% CI 0.37–0.53,  $I^2 = 0\%$ ) were inconsistent.

**Interpretation** This study showed evidence of efficacy and effectiveness of inactivated vaccines for all outcomes, although inconsistent reporting of key study parameters, high heterogeneity of observational studies, and the small number of studies of particular designs for most outcomes undermined the reliability of the findings. Findings highlight the need for additional research to address these limitations so that more definitive conclusions can be drawn to inform SARS-CoV-2 vaccine development and vaccination policies.

**Funding** Health and Medical Research Fund on COVID-19, Health Bureau of the Government of the Hong Kong SAR.

\*Corresponding author. Li Ka Shing Faculty of Medicine, Department of Pharmacology and Pharmacy, Centre for Safe Medication Practice and Research, The University of Hong Kong, L02-56 2/F, Laboratory Block, 21 Sassoon Road, Pokfulam, Hong Kong SAR, China.

\*\*Corresponding author. Li Ka Shing Faculty of Medicine, Department of Pharmacology and Pharmacy, Centre for Safe Medication Practice and Research, The University of Hong Kong, L02-56 2/F, Laboratory Block, 21 Sassoon Road, Pokfulam, Hong Kong SAR, China.

E-mail addresses: [ewchan@hku.hk](mailto:ewchan@hku.hk) (E.W.Y. Chan), [wongick@hku.hk](mailto:wongick@hku.hk) (I.C.K. Wong).

<sup>h</sup>Co-first authors.

The Lancet Regional Health - Western Pacific 2023, ■: 100788

Published Online XXX  
<https://doi.org/10.1016/j.lanwpc.2023.100788>

Copyright © 2023 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

**Keywords:** Inactivated vaccines; SARS-CoV-2; COVID; Effectiveness; Systematic review

### Research in context

Inactivated, whole-virion vaccines have been used extensively worldwide in the SARS-CoV-2 pandemic based on WHO's emergency use listing procedure. However, its real-world effectiveness across geographic regions remains to be systematically evaluated.

### Evidence before this study

Sero-surveillance research has shown lower concentration of neutralizing antibodies elicited by inactivated vaccines compared to their mRNA and recombinant counterparts. Furthermore, evidence has shown lower levels of elicited neutralizing antibodies by CoronaVac, the most widely used inactivated SARS-CoV-2 vaccine, compared to BNT162b2 against Delta and Omicron variants, suggesting greater waning of vaccine effectiveness among CoronaVac vaccinees. Notably, the most recent variant of concern (VoC), Omicron, is known to cause less severe infection but appears to be much more infectious compared to earlier variants. With emerging VoCs, the real-world effectiveness of inactivated vaccines against SARS-CoV-2 remains unclear.

### Added value of this study

This study showed evidence for efficacy and effectiveness of inactivated vaccines against infection and symptomatic disease for early SARS-CoV-2 VoC (Alpha, Delta), and for waning of vaccine effectiveness with more recent VoCs (Gamma, Omicron). Effectiveness remained relatively robust against COVID-related ICU admission and death, although estimates of effectiveness against hospitalization varied more notably across studies.

### Implications of all the available evidence

This systematic review and meta-analyses showed evidence of efficacy and effectiveness of inactivated vaccines for all study outcomes, although inconsistent reporting of key study parameters, high heterogeneity of observational studies, and the small number of studies of particular designs for most outcomes likely undermined the reliability of the findings. Findings highlight the need for additional research to address these limitations for more definitive conclusions to be drawn to inform SARS-CoV-2 vaccine development and vaccination policies.

## Introduction

Inactivated whole-virion vaccines have been used extensively in the SARS-CoV-2 pandemic. Primarily, the inactivated vaccines CoronaVac by SinoVac Biotech and BIBP-CorV by the China National Pharmaceutical Group are widely used in all World Health Organization regions.<sup>1,2</sup>

Extensive COVID-19 vaccine research and development has led to several new inactivated vaccine clinical trials with some approved in different countries. These include CoviVac, Turkovac, Fakhovac, QazCovid-In, Kconvac, CovIran, WIBP-CorV and Valneva.<sup>1</sup>

Over the course of the pandemic, sero-surveillance research has shown a lower concentration of neutralizing antibodies elicited by inactivated vaccines compared to its mRNA and recombinant counterparts.<sup>3-5</sup> Furthermore, evidence has shown significantly lower levels of elicited neutralizing antibodies by CoronaVac, the most widely used inactivated SARS-CoV-2 vaccine, compared to BNT162b2 against Delta and Omicron variants 3 months after vaccination,<sup>6</sup> suggesting greater waning of vaccine effectiveness among CoronaVac vaccinees. On the other hand, the most recent variant of concern (VoC), Omicron, is known to cause less severe infection due to its tendency to infect the upper respiratory tract. However, it is much more infectious with a higher breakthrough rate than the earlier Delta variant.<sup>7,8</sup> Against the

backdrop of emerging VoCs, the real-world effectiveness of inactivated vaccines against SARS-CoV-2 across geographic regions remains unclear. Furthermore, varying severity of infection associated with different VoCs could also mean that examining vaccine efficacy and effectiveness (VE) against symptomatic disease and infection may not be sufficiently indicative of a vaccine's protective effects.

This knowledge gap prompts a need to review and examine evidence on the clinical and real-world effectiveness of inactivated vaccines against infection, as well as severe clinical outcomes of COVID-19 such as hospitalization, critical care admission, and death in order to enable healthcare professionals and the general public to make informed choices for different vaccine platforms. In view of this, the aim of this study is to systematically review and meta-analyze published, peer-reviewed evidence on all approved inactivated vaccines, and evaluate vaccine efficacy and/or effectiveness (VE) against SARS-CoV-2 infection, symptomatic infection, severe clinical outcomes, and severe infection. In this paper, the abbreviation "VE" could stand for vaccine efficacy or vaccine effectiveness, depending on the specific study or studies under discussion. Efficacy refers to how well a vaccine performs in a controlled environment, whereas effectiveness refers to how well it performs in real world settings.<sup>9</sup> Essentially, according

to the U.S. CDC, “vaccine efficacy/effectiveness is interpreted as the proportionate reduction in disease among the vaccinated group”.<sup>10</sup>

## Methods

This study was registered with PROSPERO (CRD42022356603), where the review protocol can be accessed. The study was conducted according to the original protocol registered with PROSPERO. Results were reported following Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) 2020.

### Search strategy, data sources, and study selection

Electronic databases including Pubmed (including MEDLINE), EMBASE (via Ovid), Web of Science Core Collection, Web of Science Chinese Science Citation Database, and [Clinicaltrials.gov](https://www.clinicaltrials.gov) were searched on June 27, 2022. Search terms included the MeSH Terms and keywords: “WIBP-CorV” OR “QazCovid” OR “Covaxin” OR “CoviVac” OR “CovIran” OR “FAKHRAVAC” OR “TURKOVAC” OR “KCONVAC” OR “CoronaVac” OR “BIBP-CorV”, OR “Vaccines, Inactivated” AND “COVID-19 Vaccines” AND “effectiveness” OR “Efficacy, Vaccines” NOT “review”. For EMBASE, terms were applied to title and keywords. For Web of Science, we applied the same terms for title, abstract, and keywords.

Studies identified from the search were retrieved and screened. Full search terms are shown in [Supplement 1](#). Details of the final pool of included studies are shown in [Supplement 2](#).

### Study selection

Published, peer-reviewed quantitative studies in English or Chinese reporting effectiveness or efficacy of complete vaccination using any approved inactivated vaccine for all ages from January 1, 2019 to June 27, 2022 were included.

Conference abstracts, research letters, animal studies, recommendations, expert opinions, case reports, case series, economic evaluations, clinical guidelines, those without an unvaccinated comparator, or included only pregnant populations were excluded. Studies which did not stratify/specify samples based on the number of vaccine doses received were also excluded. Results reporting 100% VE were not included in analysis, as standard error could not be estimated. Four investigators independently determined the eligibility and inclusion of studies (ML, SH, CH, GT) in this systematic review, with discrepancies resolved through discussion.

### Data collection and risk of bias assessment

All identified potential studies were stored in Endnote 20.4. After independent title and abstract screening by

two investigators (ML, SH), full texts were reviewed and extracted using a standardized form by four investigators (ML, SH, CH, GT). The following information was extracted: year of publication, country, vaccine(s) of interest, vaccinated and unvaccinated sample size, ethnicity, population group (patient, HCW, previously infected), follow-up period (after specified regimen), age of inclusion, outcome of interest (against clinical outcomes, risk of infections/symptomatic infection, or severe SARS-Cov-2 infections), method of VE calculation, and results in the form of odds (OR), hazard (HR), incident rate (IRR), and risk ratios (RR) with inferential statistical test estimates.

Risk of bias assessment was conducted using the Cochrane Collaboration’s Risk of Bias 2 (RoB 2) tool for randomized controlled trials (RCT),<sup>11</sup> and the Newcastle–Ottawa Scale (NOS) for non-randomized observational studies.<sup>12</sup> The NOS criteria are documented in [Supplement 3](#). A star was awarded to studies that stratified results by age or adjusted for age, and another star for specifying/adjusting for a dominant variant in the study setting during the study period. For cohort studies, a star was awarded to those with a study period of 5 months, which was the median length of our final pool. For outcome assessment and adequacy of case definition, a star was awarded to studies which used real-time polymerase chain reaction (RT-PCR) as the sole method of outcome ascertainment. Under the NOS criteria, observational studies with fewer than 5 stars were graded as low, 5–7 as mid, and 8 or above as high quality.<sup>13</sup> Studies with population-based samples were given a star and those with hospital-based or healthcare worker samples were not.

### Grading the quality of evidence

The GRADE (Grading of Recommendations, Assessment, Development and Evaluations)<sup>14</sup> framework was used to assess the quality of evidence ([Supplement 4](#)). Four levels of quality were applied: very low, low, moderate, and high.

### Definitions and outcomes

The primary outcome of this study was symptomatic disease. Secondary outcomes were infection, COVID-19 related hospitalization, COVID-19 related ICU admission, COVID-19 related death, and severe infection. Consistent with the definitions used by the U.S. Food and Drug Administration and the National Health Commission of China, severe infection was defined as virologically confirmed SARS-CoV-2 infection with any of the following: (i) respiratory rate  $\geq 30$ /min, (ii) resting oxygen saturation  $\leq 93\%$ , (iii) oxygenation index  $< 300$  mm Hg, (iv) evidence of shock, (v) ICU admission, (vi) needing oxygen/mechanical ventilation, (vii) organ failure, or (viii) death. Effect measures were OR for case-control studies and RCTs, while those for cohort studies were HR, OR, or IRR.

A complete regimen of inactivated vaccine was defined as 14 days after the 2nd dose of each respective vaccine. Symptomatic SARS-CoV-2 infection was defined as RT-PCR confirmed SARS-CoV-2 infection after onset of symptoms, whereas RT-PCR confirmed SARS-CoV-2 infection included both symptomatic and asymptomatic cases.

#### Data synthesis and statistical analysis

Review Manager 5.4.1 was used to conduct the meta-analysis. Meta-analysis was used to generate estimates of VE if two or more studies could be included. Meta-analyses were stratified by study type (case-control, cohort, and RCT) and OR were pooled for meta-analysis of case-control studies. However, for cohort studies, analysis was separated by the type of risk ratio (HR, IRR, and OR) used. Relative risk was pooled alongside OR by converting the sample sizes of vaccinated and unvaccinated groups. For RCTs, the number of incident cases and vaccinated/unvaccinated sample sizes were extracted and inputted into Review Manager to calculate OR. A generic inverse variance and random effects model was used in the meta-analysis. Standard error values were calculated for each study's findings, which were then inputted into Review Manager.

For studies that only reported results stratified by age group or time-after-dose, risk ratios of the groups/results were combined using a fixed-effects model.<sup>13</sup> For studies which did not report results in ratio, the reported VE% was calculated using the equation [ratio = (1-VE)/100]. The same method was used to obtain 95% confidence intervals (CI).

Heterogeneity was evaluated using  $I^2$  expressed as percentages (low (<25%), moderate (50%), and high ( $\geq 75\%$ )).<sup>15</sup> Sensitivity analyses were conducted for meta-analyses with outlying studies, with particular attention given to changes in the  $I^2$  values, overall estimate, as well as the 95% CI. For subgroup analysis, this was done by age, VoC, and vaccine brand when two or more studies were available for inclusion in any outcome. For age groups, those <18 years were classified as children, 18–59 years as adults, and  $\geq 60$  years as older adults.

#### Role of the funding source

The funding source had no involvement in the study design, data collection, data analysis, data interpretation and writing of the manuscript. The corresponding authors had final responsibility for the decision to submit for publication.

## Results

### Search results and study selection

One thousand seven hundred and forty one records were identified for title/abstract screening after electronic removal of 162 duplicate records (Fig. 1). Of

these, one thousand five hundred and ninety records were screened and excluded from assessing for eligibility for various reasons: not studying the outcomes of interest (n = 1158), not a primary research article with collection of first-hand data (n = 234), no corresponding paper (n = 154), a duplicate that was not removed electronically in the previous step (n = 36), or other reasons (n = 8). The remaining 151 full-texts were assessed for eligibility, and 28 studies were ultimately included in our analysis (n = 32,886,885), among which there were five RCTs and 23 observational studies (Table 1). One hundred and twenty three full-texts were excluded for various reasons: no corresponding paper (n = 30), not studying the outcomes of interest (n = 29), not the correct study type (n = 21), pre-prints (n = 14), no unvaccinated comparator (n = 14), no separation by vaccine (n = 9), or other reasons (n = 6). The entries with no corresponding papers (n = 30) were [ClinicalTrials.gov](https://www.clinicaltrials.gov) entries with no published paper at the time of data analysis. One study was excluded due to reporting VE results only for a 3-dose regimen.<sup>16</sup> Two studies were excluded as the 95% CIs differed considerably from Review Manager calculations.<sup>17,18</sup> A summary table of included studies can be found in [Supplement 2](#). For included results, VE against death was excluded for one case-control study as it was reported in HR—whereas other case-control studies had reported this outcome in OR.<sup>19</sup> For studies reporting 100% VE, three results from three studies investigating VE against severe COVID-19 were excluded,<sup>20–22</sup> and efficacy from one RCT which combined VE against death and hospitalization was excluded.<sup>23</sup>

### Quality and risk of bias assessment

For cohort studies, the majority used population-based samples for exposed and unexposed groups. All studies adjusted for age, and most adjusted for or specified the dominant VoC during the study period. Furthermore, most studies used RT-PCR testing as the sole method of case ascertainment. However, reporting of follow-up periods was inconsistent, rendering evaluation of the changes in VE difficult ([Supplement 5](#)). Included case-control studies consisted largely of hospital-based samples ([Supplement 6](#)). All but one study did not adjust for age<sup>30</sup> as it only studied older adults ( $\geq 60$  years).

For RCTs, all studies used randomization to assign exposure status. One study lacked complete allocation concealment in its delivery of exposures.<sup>40</sup> All RCTs were double blinded, had a low drop-out rate (<10%), and used RT-PCR as the only method of case ascertainment. However, four studies had some concerns in the selection of reported results<sup>20,28,39,40</sup>; among which two were due to the employment of per-protocol analysis.<sup>20,39</sup> Ultimately, only one RCT achieved an overall low risk of bias,<sup>27</sup> while the other four had some overall concerns<sup>20,28,39,40</sup> ([Supplement 7](#)).

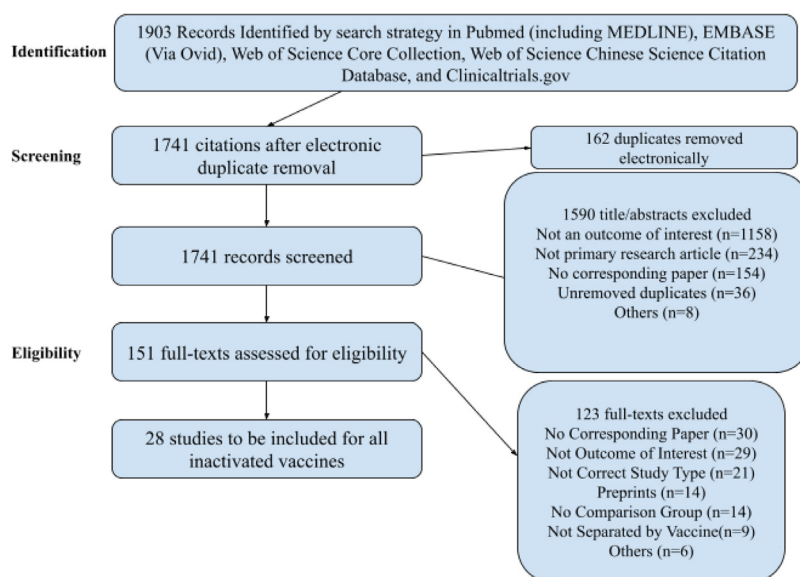


Fig. 1: PRISMA flowchart.

### Systematic review

Table 1 shows all included studies with their vaccine efficacy and effectiveness, alongside corresponding dominant variant(s), age group, and vaccine(s) of interest. No studies reported VE against symptomatic infection during Alpha or Beta-dominant periods. Studies on earlier Alpha and Delta variants tend to report significantly higher VE against symptomatic disease and infection outcomes, in comparison to studies on the later Gamma and Omicron variants, against which VE often fell below WHO's minimum requirement of 50% VE for infection and symptomatic disease.<sup>46</sup> However, this association cannot be clearly established as different vaccines of interest were used in the respective studies. Specifically, while studies on the Delta variant included both CoronaVac and BIBP-CorV, all studies including Alpha and Beta variants used only BIBP-CorV or QazCovid-In. On the other hand, all studies including the Gamma variant used CoronaVac. For Omicron, there were three studies: two used CoronaVac,<sup>42,47</sup> and a third was study that used BIBP-CorV in children.<sup>37</sup> As such, the apparent waning of effectiveness of inactivated vaccines against later variants could also be attributed to differences in VE between BIBP-CorV and CoronaVac. The only head-to-head cohort study between these two vaccines was conducted in China during a Delta-dominant period,<sup>21</sup> which showed BIBP-CorV to be superior to CoronaVac, although the study yielded highly imprecise estimates with very wide 95% CI (VE 50.56%, 95% CI 3.79–74.59% vs. VE 39.12%, 95% CI –0.91–63.27%).<sup>21</sup>

It is difficult to determine the relative superiority of VE for particular brands of inactivated vaccines due to

the absence of brand-specific studies for ICU admission outcome, and inconsistencies in VE findings against the Gamma and Omicron variants for hospitalization and death outcomes.

### Efficacy/effectiveness against symptomatic infection

Fig. 2 shows forest plots for VE of inactivated vaccines against symptomatic COVID-19 infection. Dominant variants differed across studies. Pooled case-control studies included Gamma and Delta-dominant periods, while RCTs included earlier variants or did not specify as they were conducted prior to the emergence of VoCs. Among four case-control studies, the overall effectiveness estimate was OR 0.32 (95% CI 0.16–0.64,  $I^2 = 98\%$ ). These studies reported results for CoronaVac and BIBP-CorV. Two focused on older populations ( $\geq 60$  and  $\geq 70$  years),<sup>27,28</sup> while the other two included adults of all ages ( $\geq 18$  years).<sup>31,34</sup> One of the two case-control studies on older populations reported significantly higher VE (OR 0.06, 95% CI 0.04–0.08) in comparison to other studies.<sup>28</sup> This study investigated the effectiveness of BIBP-CorV in a Delta-dominant period among older adults, while the other three studied VE of CoronaVac against Gamma and Delta periods in adults of all ages. When this study was removed, VE decreased significantly; however, the estimate became much more precise (OR 0.58, 95% CI 0.53–0.64,  $I^2 = 30\%$ ), and the quality of the case-control pool increased to “low”. One study reported the results in HR.<sup>33</sup>

Five RCTs examined this outcome.<sup>20,27,28,39,40</sup> Efficacy among RCTs was higher (OR 0.21, 95% CI 0.16–0.27,  $I^2 = 28\%$ ) than effectiveness from case-control studies.

Author	Study design	Variant of concern (VoC)	Vaccine of interest	Country	Total	Mean/median follow-up time	Population group	Symptomatic infection	Infection	Hospitalization	ICU admission	Mortality	Severe infection
Vokó et al. 2021 <sup>24</sup>	Retrospective cohort	Alpha	Sinopharm/BBIBP-CorV/BBIBP/SARS-CoV-2 Vaccine (Vero Cell)/Hayat-Vax	Hungary	4,930,041	-	General public, ≥16	-	IRR 0.313 (0.299–0.328)	-	-	IRR 0.122 (0.106–0.139)	-
Al Kaabi et al. 2022 <sup>25</sup>	Retrospective cohort	Alpha & Delta	Sinopharm/BBIBP-CorV/BBIBP/SARS-CoV-2 Vaccine (Vero Cell)/Hayat-Vax	United Arab Emirates (UAE)	2,199,772	-	General public, ≥18	-	-	HR 0.20 (0.19–0.22)	HR 0.14 (0.11–0.18)	HR 0.16 (0.09–0.29)	-
Al Hosani et al. 2022 <sup>26</sup>	Retrospective cohort	Alpha, Beta, Delta	Sinopharm/BBIBP-CorV/BBIBP/SARS-CoV-2 Vaccine (Vero Cell)/Beijing Institute of Biological Products	UAE	154,872	-	General public, ≥15	-	-	OR 0.26 (0.24–0.28)	OR 0.09 (0.07–0.12)	OR 0.09 (0.07–0.12)	-
Khairullin et al. 2022 <sup>27</sup>	RCT	Alpha, Delta	QazCovid/QazCovid-In	Kazakhstan	2835	-	General public, ≥18	OR 0.17 (0.10–0.27)	-	-	-	-	-
Ella et al. 2021 <sup>28</sup>	RCT	Alpha, Delta, and a non-VoC	Covaxin/BBV152	India	16,923	-	General public, ≥18	OR 0.23 (0.14–0.35)	OR 0.31 (0.19–0.53)	-	-	-	IRR 0.066 (0.02–0.429)
Rearte et al. 2022 <sup>29</sup>	Test-negative case control	Alpha, Gamma, and a non-VoC	Sinopharm/BBIBP-CorV/BBIBP/SARS-CoV-2 Vaccine (Vero Cell)/Hayat-Vax	Argentina	201,022	-	General public, ≥60	-	OR 0.56 (0.55–0.58)	-	-	HR 0.27 (0.25–0.29)	-
Sritipsukho et al. 2022 <sup>29</sup>	Test-negative case control	Delta	SinoVac/CoronaVac/PiCoVacc	Thailand	1795	-	General public, ≥18	-	OR 0.1240 (0.044–0.3493)	-	-	-	OR 0.1240 (0.044–0.3493)
Nadeem et al. 2022 <sup>30</sup>	Case-control study	Delta	Sinopharm/BBIBP-CorV/BBIBP/SARS-CoV-2 Vaccine (Vero Cell)/Hayat-Vax	Pakistan	3426	-	General public, ≥60	OR 0.057 (0.041–0.078)	-	OR 0.395 (0.171–0.921)	OR 0.339 (0.07–1.591)	OR 0.014 (0.004–0.058)	-
Wu et al. 2022 <sup>21</sup>	Retrospective cohort	Delta	Sinopharm/BBIBP-CorV/BBIBP/SARS-CoV-2 Vaccine (Vero Cell)/Hayat-Vax, SinoVac/CoronaVac/Picovac	China	1020	-	Close contact, ≥18	OR BIBP 0.4944 (0.2541–0.9621) OR CoronaVac 0.6088 (0.3673–1.0091)	-	-	-	-	OR BIBP 0.00 OR CoronaVac 0.00
Li et al. 2021 <sup>22</sup>	Test-negative case-control	Delta	Sinopharm/BBIBP-CorV/BBIBP/SARS-CoV-2 Vaccine (Vero Cell)/Hayat-Vax, SinoVac/CoronaVac/PiCoVacc	China	253	-	Close contact, 18–59	-	OR 0.41 (0.19–0.84)	-	-	-	OR BIBP 0.00 OR CoronaVac 0.00
Cerqueira-Silva et al. 2022 <sup>31</sup>	Test-negative case control	Delta and Gamma	SinoVac/CoronaVac/PiCoVacc	Brazil	121,371	-	Previously infected, ≥18	OR 0.606 (0.574–0.639)	-	-	-	-	-
Cerqueira-Silva et al. 2022 <sup>32</sup>	Test negative case control	Delta and Gamma	SinoVac/CoronaVac/PiCoVacc	Brazil	3,574,614	-	General public, ≥18	-	OR 0.52 (0.52–0.53)	-	-	-	-
Can et al. 2022 <sup>33</sup>	Retrospective cohort	Delta and Gamma	SinoVac/CoronaVac/PiCoVacc	Turkiye	3174	-	Healthcare workers, ≥15	HR 0.610 (0.463–0.804)	-	-	-	-	-
Hitchings et al. 2021 <sup>34</sup>	Test-negative case control	Gamma	SinoVac/CoronaVac/PiCoVacc	Brazil	343	14 days	Healthcare workers, ≥18	OR 0.63 (0.26–1.53)	-	-	-	-	-
Ranzani et al. 2021 <sup>35</sup>	Test-negative case control	Gamma	SinoVac/CoronaVac/PiCoVacc	Brazil	39,816	-	General public, ≥70	OR 0.532 (0.462–0.613)	-	OR 0.445 (0.371–0.535)	-	OR 0.388 (0.295–0.511)	-
Marra et al. 2022 <sup>36</sup>	Retrospective cohort	Gamma	SinoVac/CoronaVac/PiCoVacc	Brazil	7897	-	Healthcare workers, ≥18	IRR 0.487 (0.363–0.654)	-	-	-	-	-

(Table 1 continues on next page)

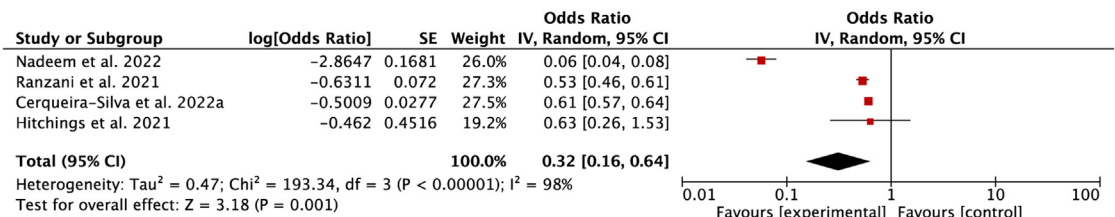


Author	Study design	Variant of concern (VoC)	Vaccine of interest	Country	Total	Mean/median follow-up time	Population group	Symptomatic infection	Infection	Hospitalization	ICU admission	Mortality	Severe infection
(Continued from previous page)													
Arregoces-Castillo et al. 2022 <sup>23</sup>	Retrospective cohort	Non-VoC	SinoVac/CoronaVac/PiCoVacc	Colombia	2,097,431	-	General public, ≥60	-	-	OR 0.35 (0.33-0.37)	-	OR 0.30 (0.28-0.32)	-
Gonzalez et al. 2022 <sup>27</sup>	Retrospective cohort	Omicron	Sinopharm/BBIBP-CorV/BIBP/SARS-CoV-2 Vaccine (Vero Cell)/Hayat-Vax	Argentina	726,954	110 (±19) days	Close contact, 3-11	-	-	OR 0.236 (0.165-0.371)	-	-	-
Jara et al. 2022 <sup>38</sup>	Retrospective cohort	Omicron	SinoVac/CoronaVac/PiCoVacc	Chile	383,950	-	General public, 3-5	HR 0.618 (0.601-0.635)	-	HR 0.354 (0.248-0.504)	HR 0.310 (0.118-0.814)	-	-
Suah et al. 2022 <sup>39</sup>	Retrospective cohort	Omicron	SinoVac/CoronaVac/PiCoVacc	Malaysia	5,650,550	-	General public, ≥15	-	OR 0.41 (0.37-0.46)	-	OR 0.48 (0.44-0.53)	OR 0.21 (0.19-0.24)	-
Fadlyana et al. 2021 <sup>40</sup>	RCT	Unspecified	SinoVac/CoronaVac/PiCoVacc	Indonesia	1620	Vaccinated: 80.78 days Placebo: 72.08 days	General public, ≥19	OR 0.39 (0.16-0.93)	-	-	-	-	OR 0.00
Suah et al. 2021 <sup>41</sup>	Retrospective cohort	Unspecified	SinoVac/CoronaVac/PiCoVacc	Malaysia	977,004	-	General public, ≥20	-	-	-	IRR 0.28 (0.261-0.301)	IRR 0.176 (0.163-0.19)	-
Jara et al. 2021 <sup>42</sup>	Prospective cohort	Unspecified	SinoVac/CoronaVac/PiCoVacc	Chile	9,645,302	-	General public, ≥16	-	HR 0.363 (0.354-0.372)	HR 0.135 (0.126-0.144)	HR 0.098 (0.086-0.111)	HR 0.133 (0.117-0.151)	-
Mirahmadizadeh et al. 2022 <sup>43</sup>	Retrospective cohort	Unspecified	Sinopharm/BBIBP-CorV/BIBP/SARS-CoV-2 Vaccine (Vero Cell)/Hayat-Vax, CovIran/BIV1-CovIran (Barakat/Barkat)	Iran	1,736,773	105 days	General public, ≥18	-	BIBP-CorV: IRR 0.211 (0.196-0.206) CovIran: IRR 0.129 (0.117-0.140)	BIBP-CorV: IRR 0.281 (0.269-0.293) CovIran: IRR 0.136 (0.112-0.159)	-	BIBP-CorV: IRR 0.139 (0.120-0.159) CovIran: IRR 0.027 (0-0.037)	-
Tanriover et al. 2021 <sup>39</sup>	RCT	Unspecified	SinoVac/CoronaVac/PiCoVacc	Turkiye	10,214	43 days	General public, 18-59	OR 0.11 (0.05-0.23)	-	-	-	-	-
Al Kaabi et al. 2021 <sup>20</sup>	RCT	Unspecified	Sinopharm/BBIBP-CorV/BIBP/SARS-CoV-2 Vaccine (Vero Cell)/Hayat-Vax, WIBP/WIBP-CorV	Egypt, UAE, Bahrain, Jordan	38,206	77 days	General public, ≥18	OR WIBP 0.27 (0.17-0.43) OR BIBP 0.22 (0.13-0.37)	OR WIBP 0.36 (0.24-0.54) OR BIBP 0.27 (0.17-0.41)	-	-	-	OR 0.00
Behera et al. 2022 <sup>44</sup>	Test-negative case-control	Unspecified	Covaxin/BBV152	India	645	-	Healthcare workers, ≥18	-	OR 0.71 (0.47-1.08)	-	-	-	-
Petrovic et al. 2022 <sup>45</sup>	Retrospective cohort	Unspecified	Sinopharm/BBIBP-CorV/BIBP/SARS-CoV-2 Vaccine (Vero Cell)/Hayat-Vax	Serbia	359,080	-	General public, ≥60	-	OR 0.13 (0.12-0.14)	-	-	-	OR 0.10 (0.08-0.11)

Variants include Alpha, Beta, Delta, Gamma, and Omicron. Although several studies investigated not only inactivated vaccines, only vaccines included in this systematic review and meta-analysis are listed under "Vaccine of interest".

**Table 1: Characteristics of included studies.**

## Symptomatic infection in case-control studies



## Symptomatic infection in RCTs

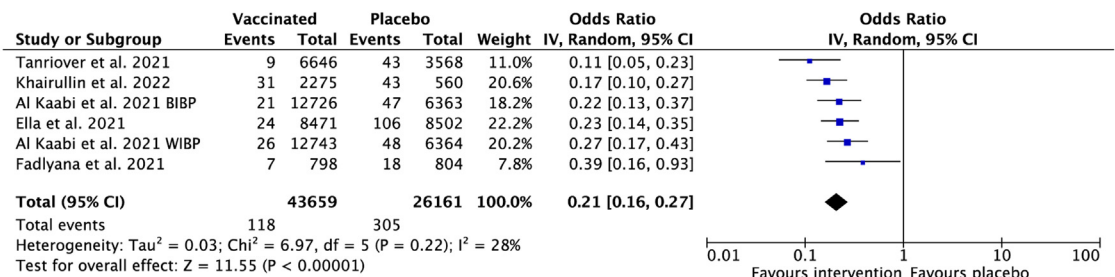


Fig. 2: Forest plot of overall estimates of VE against symptomatic SARS-CoV-2 infection.

Five RCTs reported results for QazCovid-In, Covaxin, CoronaVac, BIBP-CorV, and WIBP-CorV. All included RCTs studied the adult population (18–59 or  $\geq 18$  years), including VE against Alpha, Beta, and Delta variants. Under GRADE assessment (Supplement 8), the quality of evidence was rated as very low for case-control studies and high for RCTs.

Efficacy from four RCTs<sup>20,28,39,40</sup> against symptomatic disease among the 18–59 age group was similar to primary analysis (OR 0.23, 95% CI 0.18–0.30, I<sup>2</sup> = 0%). Two studies looked at CoronaVac.<sup>39,40</sup> (OR 0.23, 95% CI 0.09–0.59, I<sup>2</sup> = 62%). Among three case-control studies,<sup>31,34,35</sup> two included a Gamma-dominant period,<sup>34,35</sup> from which a similarly low VE estimate was found (OR 0.53, 95% CI 0.46–0.61, I<sup>2</sup> = 0%).

## Efficacy/effectiveness against infection

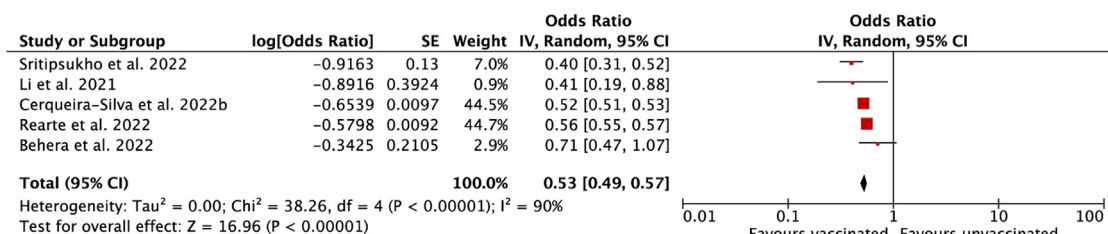
Fig. 3 shows forest plots for VE of inactivated vaccines against SARS-CoV-2 infection. Among five case-control studies,<sup>19,22,29,32,44</sup> the overall estimate for VE was OR 0.53 (95% CI 0.49–0.57, I<sup>2</sup> = 90%), reporting results for Covaxin, CoronaVac, and BIBP-CorV. Two of the five studies accounted for 89.2% of the weighting. One studied VE against infection among older adults (aged  $\geq 60$ ), while the other studied those aged  $\geq 18$ <sup>19,32</sup>; both reported similar effectiveness (0.52, 95% CI 0.51–0.53%

vs. 0.56, 95% CI 0.55–0.57%). These studies were conducted during Gamma-dominant periods. The three other studies investigated VE among those aged  $\geq 18$  or 18–59. This differed from the VE estimate of all the other 3 pools. One case-control study reported in OR and could not be pooled with other studies.<sup>19</sup>

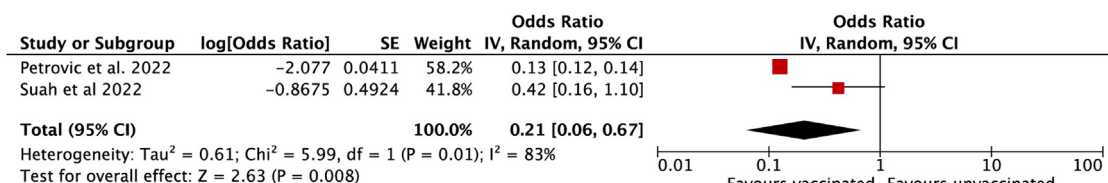
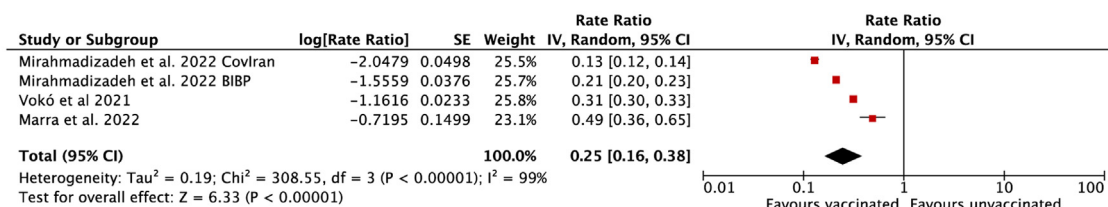
Three cohort-IRR studies reported high effectiveness for CovIran, CoronaVac, and BIBP-CorV (IRR 0.25, 95% CI 0.16–0.38, I<sup>2</sup> = 99%).<sup>24,36,43</sup> These studies included ages  $\geq 16$  or  $\geq 18$ . However, one study was conducted during an Alpha-dominant period,<sup>24</sup> while another was conducted during a Gamma-dominant period.<sup>36</sup> The study reporting highest effectiveness studied both CovIran and BIBP-CorV, reporting an effectiveness of IRR 0.129 (0.117–0.140) for CovIran and IRR 0.211 (0.196–0.206) for BIBP-CorV.<sup>43</sup> On the other hand, two cohort-OR studies reported a similar estimate for CoronaVac and BIBP-CorV (OR 0.21, 95% CI 0.06–0.67, I<sup>2</sup> = 83%).<sup>45,47</sup> However, the two studies reported significantly different results. One study reported OR 0.13 (0.12–0.14),<sup>45</sup> while the other reported OR 0.42 (0.16–1.10).<sup>47</sup> Higher VE was reported in older adults (age  $\geq 60$ ) against the Delta variant, while lower VE was reported in adults ( $\geq 18$ ) and older adults against the Omicron variant. Two RCTs reported efficacy for Covaxin, BIBP-CorV and WIBP-CorV.<sup>20,28</sup> This efficacy



### Infection in case-control studies



### Infection in cohort studies



### Infection in RCTs

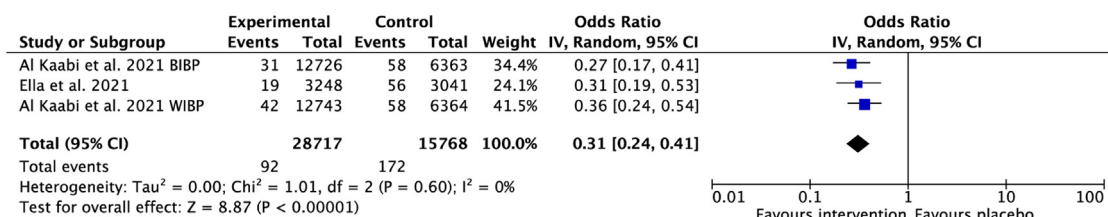


Fig. 3: Forest plot of overall estimates of VE against SARS-COV-2 infection.

estimate was consistent with effectiveness estimates from cohort pools (OR 0.27, 95% CI 0.21–0.34, I<sup>2</sup> = 0%). Both RCTs studied those aged ≥18; however, one did not specify the dominant variant.<sup>20</sup> The other included Beta and Delta-dominant periods.<sup>28</sup> Using GRADE guidelines (Supplement 8), pools for the infection outcome are of very low quality for case-controls, cohort ORs, and cohort IRRs and high quality for RCTs.

For additional analysis, VE against infection among adults was similar to primary analysis from cohort-IRR studies (IRR 0.16, 95% CI 0.11–0.22, I<sup>2</sup> = 93%).<sup>24,43</sup> One study included an Alpha-dominant period,<sup>24</sup> while the other did not specify the dominant variant. Both studies included BIBP-CorV, while one included Cov-Iran.<sup>43</sup> The same studies found lower VE against infection among older adults (IRR 0.42, 95% CI 0.23–0.80,

$I^2 = 99\%$ ). This is similar to estimates from two case-control studies which reported similar VE among older adults (OR 0.56, 95% CI 0.56–0.57,  $I^2 = 0\%$ ).<sup>19,32</sup> Conversely, when results on CovIran were removed to study brand-specific effectiveness, VE of BIBP-CorV was higher (IRR 0.26, 95% CI 0.17–0.38,  $I^2 = 99\%$ ). Meanwhile, VE of CoronaVac was found to have an OR 0.47 (95% CI 0.37–0.60,  $I^2 = 75\%$ )<sup>29,32</sup> among adult and older adult populations against Gamma and Delta periods, which was similar to the VE estimate against infection from two case-control studies conducted in Delta-dominant periods (OR 0.40, 95% CI 0.31–0.51,  $I^2 = 0\%$ ).<sup>22,29,32</sup>

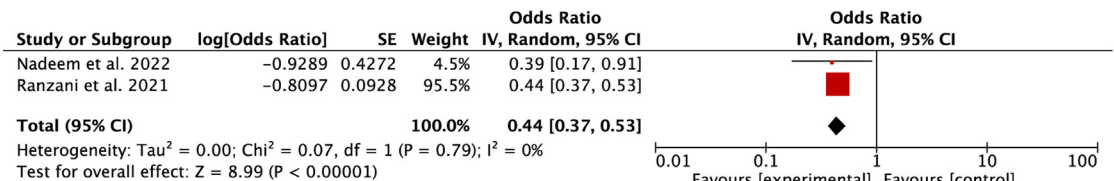
### Effectiveness against hospitalization

Fig. 4 shows the forest plot for inactivated vaccine effectiveness against COVID-19 related hospitalization. Estimates from four cohort-HR studies yielded a high VE (HR 0.24, 95% CI 0.15–0.37,  $I^2 = 99\%$ ),<sup>23,25,38,42</sup> however, the meta-analysis was of poor consistency with  $I^2 = 99\%$ . One study reported results for a pediatric population (3–5 years),<sup>42</sup> while another reported VE for an older adult population ( $\geq 60$  years).<sup>23</sup> The other two studies reported results for samples aged  $\geq 18$  and  $\geq 16$

years. Study periods had different dominant VoCs, including Alpha, Delta, Gamma, and Omicron variants. VE was similarly observed in the cohort-OR pool (OR 0.26, 95% CI 0.24–0.28,  $I^2 = 0\%$ ), however the estimate from two case-control studies differed significantly (OR 0.44, 95% CI 0.37–0.53,  $I^2 = 0\%$ ).<sup>26,37</sup> The case-control studies reported VE of CoronaVac and BIBP-CorV against the Gamma and Delta variant, among samples of age  $\geq 70$  and  $\geq 60$ , respectively. These results were similar to the findings of the older adult study ( $\geq 60$  years) in the cohort-HR pool.<sup>23</sup> Using GRADE guidelines (Supplement 8), the pools for the hospitalization outcome are of very low quality for case-control and cohort HRs, and low quality for cohort ORs.

Subgroup analyses were conducted for the older adult and CoronaVac subgroups, respectively. Both subgroups were taken from the cohort-HR pool. VE was similarly observed among both subgroups and the primary analysis, with a pool of three cohort-HR studies estimating VE against hospitalization among older adults with a HR 0.25 (95% CI 0.14–0.47,  $I^2 = 99\%$ ),<sup>23,25,38</sup> and VE of CoronaVac against hospitalization with a HR 0.25 (95% CI 0.12–0.54,  $I^2 = 100\%$ ).<sup>23,38,42</sup>

### Related hospitalization in case-control studies



### Related hospitalization in cohort studies

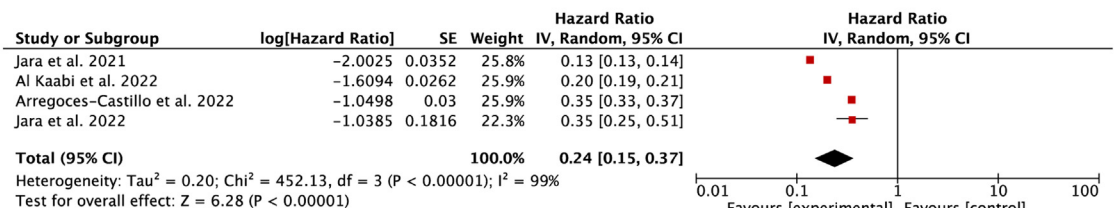
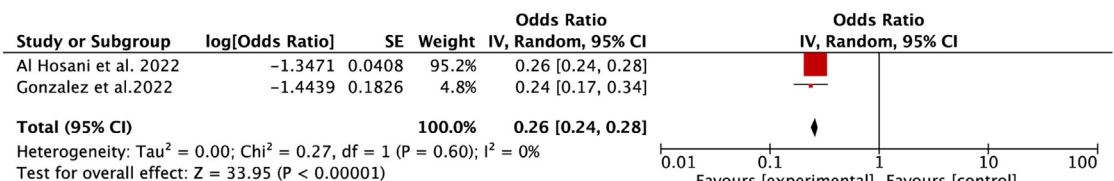


Fig. 4: Forest plot of overall estimates of VE against SARS-COV-2-related hospitalization.

**Effectiveness against ICU admission**

Fig. 5 shows the forest plot for inactivated vaccine effectiveness against COVID-19 related ICU admission. Among two cohort-OR studies,<sup>26,47</sup> VE against COVID-19 related ICU admissions was estimated to have an OR 0.21 (95% CI 0.04–1.08,  $I^2 = 99%$ ) for CoronaVac and BIBP-CorV, respectively, with significantly different findings. One study reported OR of 0.09 (95% CI 0.07–0.12),<sup>26</sup> while another reported 0.48 (0.44–0.52).<sup>47</sup> Both studies investigated samples aged  $\geq 15$ . Higher VE was reported from the study during Alpha, Beta and Delta-dominant periods using BIBP-CorV,<sup>26</sup> while lower VE was reported during an Omicron-dominant period using CoronaVac.<sup>47</sup>

Within the cohort-HR pool, three studies reported high VE for CoronaVac and BIBP-CorV (HR 0.13, 95% CI 0.09–0.19,  $I^2 = 82%$ ).<sup>25,38,42</sup> One was a pediatric study,<sup>42</sup> while the other two studied those aged  $\geq 16$  and  $\geq 18$ . After removing the pediatric study, VE remained relatively unchanged (0.12, 95% CI 0.08–0.16,  $I^2 = 85%$ ). The study periods overlapped with Alpha, Delta, Gamma and Omicron-dominant periods. However, the study which investigated an Omicron-dominant period reported significantly lower VE (HR 0.31, 95% CI 0.12–0.81)<sup>42</sup> compared to those during Alpha, Beta and Delta periods. Using GRADE guidelines (Supplement 8), both pools for ICU admission are of very low quality.

High effectiveness against ICU admission was found for both older adults<sup>25,38</sup> and CoronaVac subgroups (0.12, 95% CI 0.09–0.17,  $I^2 = 65%$  and 0.16, 95% CI 0.05–0.48,  $I^2 = 81%$ , respectively).<sup>38,42</sup> Both subgroups included two studies from the cohort-HR pool. The CoronaVac subgroup included one pediatric study during the Omicron-dominant period,<sup>42</sup> and one adult study that did not specify the dominant VoC.<sup>38</sup>

**Effectiveness against death**

Fig. 6 shows the forest plots for inactivated vaccine effectiveness against COVID-19 related death. In the cohort pool, VE against COVID-19 related death was estimated as IRR 0.10 (95% CI 0.06–0.16,  $I^2 = 97%$ ),<sup>24,41,43</sup> HR 0.19 (95% CI 0.10–0.36,  $I^2 = 98%$ ),<sup>23,25,38</sup> and OR 0.13 (95% CI 0.03–0.57,  $I^2 = 60%$ ).<sup>26,47</sup> Among the case-control studies, this was 0.08 (95% CI 0.00–2.02,  $I^2 = 96%$ ).<sup>30,35</sup> Both case-control studies investigated older adult populations ( $\geq 70$  and  $\geq 60$ ) and showed significantly different results. Higher VE was reported for BIBP-CorV against the Delta variant (0.01, 95% CI 0.00–0.05)<sup>30</sup> in comparison to CoronaVac against the Gamma variant (0.39, 95% CI 0.30–0.51).<sup>35,42</sup> At the same time, two cohort-OR studies reported vastly different results with much lower (60%) heterogeneity. Among them were samples of  $\geq 18$  and  $\geq 15$  years. One study looked at CoronaVac but did not specify the dominant variant during the study period.<sup>47</sup> The other study looked at BIBP-CorV against the Alpha, Beta and Delta variants.<sup>26</sup> A single case-control study was reported in HR and could not be pooled.<sup>19</sup>

For the cohort-IRR pool, three studies reported VE on CovIran, CoronaVac, and BIBP-CorV, investigating age groups  $\geq 18$  and  $\geq 16$ . One studied VE of BIBP-CorV against the Alpha variant,<sup>24</sup> while this was not specified in the other two studies. On the other hand, the three studies in the cohort-HR pool reported VE on CoronaVac and BIBP-CorV only. Studies investigated age groups  $\geq 16$ ,  $\geq 18$ , and  $\geq 60$ . Another study reported VE of BIBP-CorV against Alpha and Delta variants,<sup>25</sup> while one study did not specify variant type.<sup>38</sup>

Under GRADE guidelines (Supplement 8), all pools for death are of very low quality. The cohort-OR pool and case-control pool have very wide CIs, with included studies reporting significantly different results. However,

**Related ICU admission in cohort studies**

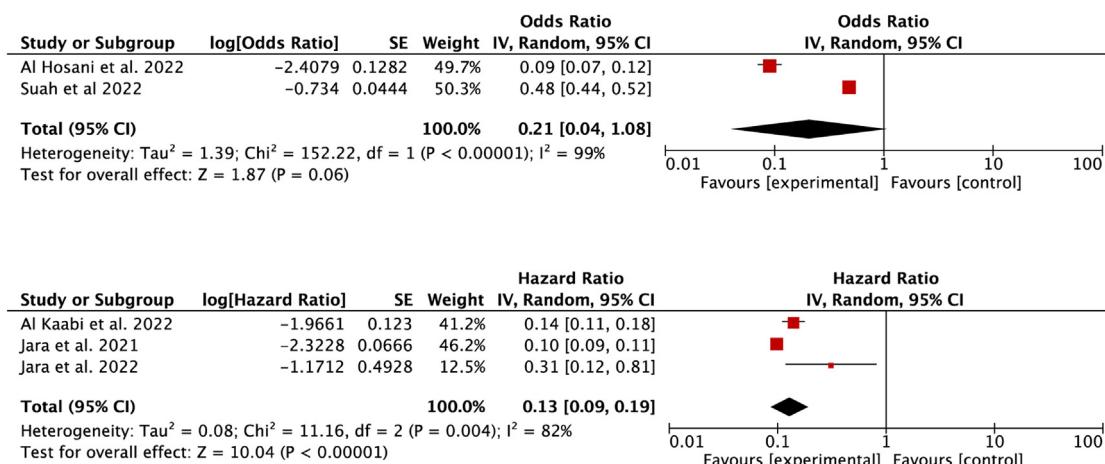
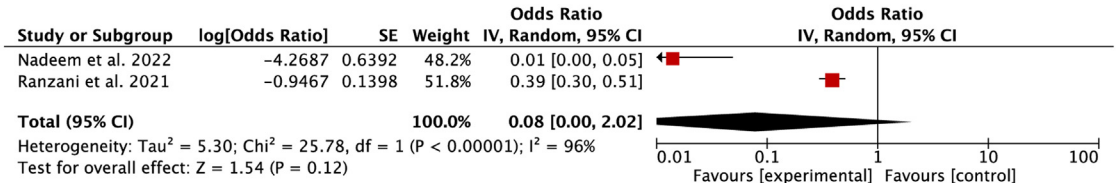


Fig. 5: Forest plot of overall estimates of VE against SARS-COV-2-related ICU admission.

### Related death in case-control studies



### Related death in cohort studies

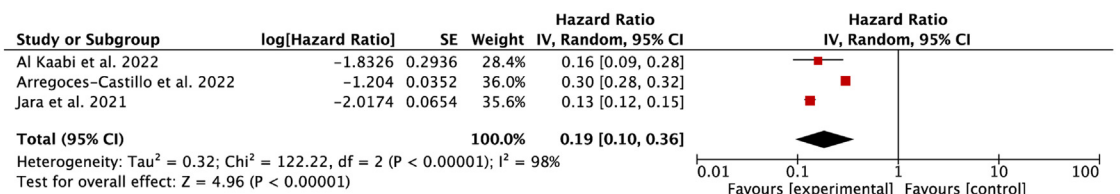
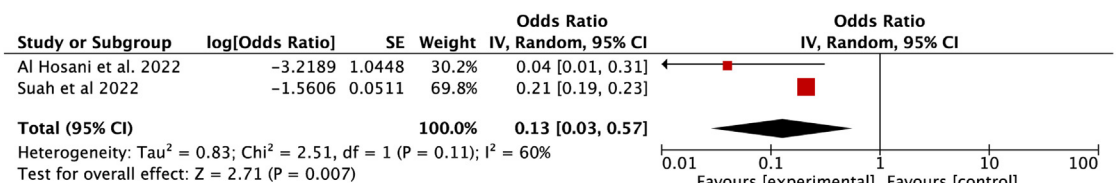
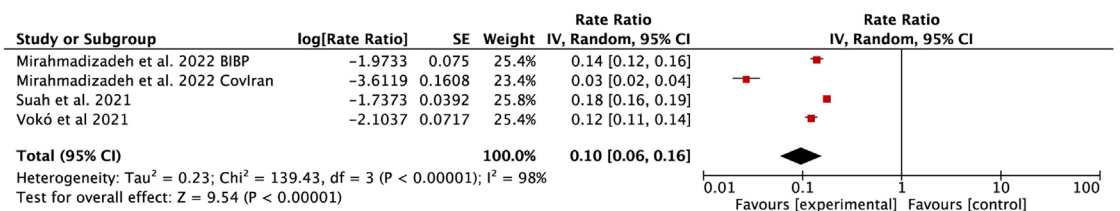


Fig. 6: Forest plot of overall estimates of VE against SARS-COV-2-related death.

estimates for this outcome were relatively consistent across design. In comparison to other outcomes, inactivated vaccines seem to have consistently higher effectiveness against COVID-19 related death.

VE against death was consistently high among subgroups. For older people, there was an IRR 0.11 (95% CI 0.07–0.16, I<sup>2</sup> = 87%)<sup>24,43</sup> and HR 0.20 (95% CI 0.10–0.39, I<sup>2</sup> = 98%),<sup>23,25,38</sup> respectively. Similarly, VE of BIBP-CorV and CoronaVac against death was OR 0.13 (95% CI 0.11–0.15, I<sup>2</sup> = 37%)<sup>24,43</sup> and HR 0.20 (95% CI 0.09–0.45, I<sup>2</sup> = 100%),<sup>23,38</sup> respectively. All studies available for subgroup analysis of this outcome specified only early variants (Alpha, Delta).

#### Effectiveness against severe COVID-19

There were too few studies to conduct meta-analysis for severe infection. In total, there were two case-control

studies,<sup>22,29</sup> two cohort studies,<sup>21,45</sup> and three RCTs<sup>20,28,40</sup> which examined this outcome. One case-control,<sup>22</sup> two cohort studies,<sup>21,45</sup> and two RCTs<sup>20,40</sup> reported 100% VE, making them ineligible for meta-analysis, while other studies reported very high VE against severe COVID-19. These studies included Delta-dominant periods but one also included the Alpha variant.

#### Discussion

This systematic review which included 28 studies with over 32 million individuals showed significantly different real-world effectiveness of inactivated vaccines against symptomatic disease and infection. It is evident that observational studies are heavily affected by confounding factors such as dominant variant, vaccine brand, and population. This also led to high heterogeneity among

them. Few studies reported variant-specific effectiveness, and many had multiple dominant strains present during the study period, further limiting the interpretability of subgroup analysis.

However, evidence supporting moderate to high effectiveness of inactivated vaccines against severe outcomes of COVID-19 was also found. Despite high heterogeneity for each individual meta-analysis, pools across case-control and cohort studies for VE against ICU admission and death outcomes yielded more consistent estimates. However, for hospitalization, there remains significant difference between VE estimates of case-control and cohort studies.

It was not feasible to generate estimates on variant-specific pooled VE for all outcomes, as many studies had included multiple dominant variants during the study period, and/or did not specify the dominant variant. Several studies, particularly the early RCTs, were conducted prior to the emergence of VoC. However, in view of the discrepancy between VE against symptomatic disease and infection from early RCTs and more recent observational studies, as well as the reduction in VE for these two outcomes against the Omicron and Gamma variants,<sup>37,42,47</sup> there is evidence to suggest waning of protection from inactivated vaccines. However, these findings may be driven by the brand-specific effectiveness of CoronaVac and BIBP-CorV as recent research on inactivated vaccines have been heavily focused on these two brands.

Analysis for the pediatric subgroup was not conducted due to the small number of studies. Moderate to high VE of inactivated vaccines against symptomatic infection and infection among the adult subgroup was found. This was ascertained from four RCTs for the primary outcome. However, VE among older adult populations for the primary outcome remains uncertain due to its wide 95% CI with the upper bound being >1. On the other hand, VE against infection among older adults was IRR 0.42 (95% CI 0.23–0.80) from two cohort studies and OR 0.56 (95% CI 0.56–0.57) from two case-control studies, compared to IRR 0.16 (95% CI 0.11–0.22) among adults. This is consistent to findings of decreasing seropositivity with age among immunogenicity research,<sup>48–50</sup> and is further supported by current findings on severe COVID-19 outcomes. However, the wide 95% CI for VE among older adults creates uncertainty in whether the trend is consistent with the results of existing research.

Vaccine-specific effectiveness estimates were only available for CoronaVac and BIBP-CorV due to a lack of published research on the other approved inactivated vaccines. Our study pool is largely represented by studies on the VE of CoronaVac and BIBP-CorV, hence overall estimates are highly similar to brand-specific estimates for these two vaccines. Only five studies investigated VE of other approved inactivated vaccines, specifically QazCovid-In, Covaxin, Coviran, and WIBP-CorV.

However, this representation could also reflect the global use of inactivated vaccines, with CoronaVac and BIBP-CorV accounting for over half of all COVID vaccine doses delivered globally,<sup>51</sup> demonstrating the current global VE of inactivated vaccines.

To our best knowledge, this is the first study to systematically review and evaluate the protective effects of the inactivated vaccine platform on the COVID-19 pandemic. Many included studies drew data from population-based sources such as national databases, providing large sample sizes and increasing external validity for the current findings. Furthermore, the pools included studies conducted in various geographic locations where inactivated vaccines were used, including Asia, the Middle East, Europe and South America. Only one observational study was rated as of low quality under the NOS, and we have high confidence in our estimates on the efficacy of inactivated vaccines against symptomatic SARS-CoV-2 infection and infection. We were also able to extensively study VE among adult and older adult subgroups and obtained brand-specific VE estimates for the two most widely used inactivated vaccines (i.e., CoronaVac and BIBP-CorV).

This study has several limitations. Firstly, we were unable to use follow-up periods to evaluate waning effectiveness due to inconsistent reporting, and a vast majority of our pool consisted of case-control studies. We were only able to assess changes in VE by comparing studies published during different time points/dominant variants in the pandemic, which showed decrease in VE for symptomatic infection and infection outcomes against more recent variants (Gamma, Omicron). Secondly, the high heterogeneity ( $I^2 > 75\%$ ) in all observational pools significantly reduced the precision of our estimates according to GRADE guidelines. Pooled studies often differed by vaccine of interest, variant present, and population characteristics. For severe outcomes, heterogeneity could also have been caused by varying definitions of “COVID-19 related” hospitalization, ICU admission, or death. Furthermore, the evaluation of publication bias was not possible as no pool had 10 or more studies. Symptomatic disease and infection outcomes are prone to underrepresentation due to surveillance bias resulting from factors such as reluctance to test for COVID-19.<sup>52</sup> Thirdly, this study only included peer-reviewed publications. It excluded some of the earliest evidence on inactivated vaccines, many of which were RCTs published as pre-prints for emergency approvals during the early stage of the pandemic.<sup>53</sup> Finally, this study only examined the efficacy and effectiveness of complete vaccination, that is, completing the primary vaccination series. It did not examine the efficacy and effectiveness of booster doses for those who completed a primary series of inactivated vaccines, as the data were scarce when this study was completed. However, the findings shed light on the strengths and weaknesses of



inactivated vaccines before boosters became widely available. Two of the included studies investigated the effectiveness of booster doses to those already fully vaccinated with inactivated vaccines (BIBP-CorV and CoronaVac). Their findings suggest that a homologous or heterologous booster dose led to greater VE against later VoCs compared to the primary series only.<sup>29,32</sup> More recent studies show that heterologous boosting appears to be superior in effectiveness compared to homologous boosting.<sup>54,55</sup>

In conclusion, while observational studies and clinical trials reported high VE of inactivated vaccines against infection and symptomatic disease for early SARS-CoV-2 VoC (Alpha, Delta), there is evidence to suggest waning of vaccine effectiveness with more recent VoCs (Gamma, Omicron), although this finding may be driven by brand-specific effectiveness due to differences in the volume of research for different inactivated vaccines. On the other hand, effectiveness has remained relatively robust against COVID-19 related ICU admission and death, although VE estimates against hospitalization are inconsistent. These findings highlight the need for further research regarding booster vaccination and heterologous dosing, especially for those who were initially given inactivated vaccines. They also raise questions about the robustness of inactivated vaccines against new SARS-CoV-2 variants. Further evidence on the safety of inactivated vaccines is also needed to assess the risks and benefits of inactivated vaccines in the SARS-CoV-2 pandemic and to inform vaccination policies.

#### Contributors

ICKW and EWC conceived and designed the study. ML, SH, GT and CH conducted the database search, performed the initial screening, extraction of full texts for determining eligibility, and completed the quality assessment. ML, SH and FL conducted the meta-analyses. ML, SH, CK, VY, EY and FL interpreted the findings. ML and SH drafted the manuscript and prepared the figures and tables. ICKW and EWC provided study oversight. All authors have reviewed and approved the final manuscript.

#### Data sharing statement

As this study is a systematic review and meta-analysis of published studies, all data are publicly available in the specified references.

#### Ethics approval

None.

#### Declaration of interests

FTTL has been supported by the RGC Postdoctoral Fellowship under the Hong Kong Research Grants Council and has received research grants from the Health Bureau of the Government of the Hong Kong Special Administrative Region, outside the submitted work. ICKW receives research funding outside the submitted work from Amgen, Bristol-Myers Squibb, Pfizer, Janssen, Bayer, GSK, Novartis, the Hong Kong Research Grants Council, the Health Bureau of the Government of the Hong Kong Special Administrative Region, National Institute for Health Research in England, European Commission, and the National Health and Medical Research Council in Australia; has received consulting fees from the World Health Organization and IQVIA; and is an independent non-executive director of Jacobson Medical in Hong Kong. EWC has received grants from Research Grants Council (RGC, Hong Kong

Special Administrative Region), Health Bureau of the Government of the Hong Kong Special Administrative Region, National Natural Science Fund of China, Bayer, Bristol-Myers Squibb, Pfizer, Janssen, Novartis, Amgen, AstraZeneca, Takeda, the RGA Reinsurance Company, Narcotics Division of the Security Bureau of the Hong Kong Special Administrative Region; consulting fees from AstraZeneca, Pfizer and Novartis; and honorarium from the Hospital Authority Hong Kong, outside the submitted work. All other authors declare no competing interests.

#### Acknowledgements

The authors acknowledge Lisa Lam for proofreading and colleagues at the Centre for Safe Medication Practice and Research of the Department of Pharmacology and Pharmacy at the University of Hong Kong for their input and insights regarding data analyses and interpretation.

#### Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jlanwpc.2023.100788>.

#### References

- 1 Approved vaccines [Internet]. Available from: VIPER Group COVID19 Vaccine Tracker Team; 2022. <https://covid19.trackvaccines.org/vaccines/approved/#vaccine-list>. Accessed August 2, 2022.
- 2 Countries [Internet]. Available from: World Health Organisation; 2022. <https://www.who.int/countries>. Accessed August 2, 2022.
- 3 Lim WW, Mak L, Leung GM, Cowling BJ, Peiris M. Comparative immunogenicity of mRNA and inactivated vaccines against COVID-19. *Lancet Microbe*. 2021;2(9):e423.
- 4 Angkasekwinai N, Sewatanon J, Niyomnaitam S, et al. Comparison of safety and immunogenicity of CoronaVac and ChAdOx1 against the SARS-CoV-2 circulating variants of concern (Alpha, Delta, Beta) in Thai healthcare workers. *Vaccine X*. 2022;10:100153.
- 5 Mok CKP, Cohen CA, Cheng SMS, et al. Comparison of the immunogenicity of BNT162b2 and CoronaVac COVID-19 vaccines in Hong Kong. *Respirology*. 2022;27(4):301–310.
- 6 Peng Q, Zhou R, Wang Y, et al. Waning immune responses against SARS-CoV-2 variants of concern among vaccinees in Hong Kong. *eBioMedicine*. 2022;77:103904.
- 7 Hui KPY, Ho JCW, Cheung MC, et al. SARS-CoV-2 Omicron variant replication in human bronchus and lung ex vivo. *Nature*. 2022;603(7902):715–720.
- 8 Goga A, Bekker L-G, Garrett N, et al. Breakthrough SARS-CoV-2 infections during periods of delta and omicron predominance, South Africa. *Lancet*. 2022;400(10348):269–271.
- 9 Weinberg GA, Szilagyi PG. Vaccine epidemiology: efficacy, effectiveness, and the translational research roadmap. *J Infect Dis*. 2010;201(11):1607–1610.
- 10 Principles of epidemiology [Internet]. Available from: Centers for Disease Control and Prevention; 2012. <https://www.cdc.gov/csels/dsepd/ss1978/lesson3/section6.html>. Accessed January 29, 2023.
- 11 Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
- 12 Wells G, Shea B, O'Connell D, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis [Internet]. Available from: [https://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). Accessed August 2, 2022.
- 13 Ssentongo P, Ssentongo AE, Voleti N, et al. SARS-CoV-2 vaccine effectiveness against infection, symptomatic and severe COVID-19: a systematic review and meta-analysis. *BMC Infect Dis*. 2022;22(1):439.
- 14 Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924–926.
- 15 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557–560.
- 16 Jara A, Undurraga EA, Zubizarreta JR, et al. Effectiveness of homologous and heterologous booster doses for an inactivated SARS-CoV-2 vaccine: a large-scale prospective cohort study. *Lancet Glob Health*. 2022;10(6):e798–e806.
- 17 Hu Z, Tao B, Li Z, et al. Effectiveness of inactivated COVID-19 vaccines against severe illness in B.1.617.2 (Delta) variant-infected patients in Jiangsu, China. *Int J Infect Dis*. 2022;116:204–209.



- 18 Kang M, Yi Y, Li Y, et al. Effectiveness of inactivated COVID-19 vaccines against illness caused by the B.1.617.2 (Delta) variant during an outbreak in Guangdong, China: a cohort study. *Ann Intern Med.* 2022;175(4):533–540.
- 19 Rearte A, Castelli JM, Rearte R, et al. Effectiveness of rAd26-rAd5, ChAdOx1 nCoV-19, and BBIBP-CorV vaccines for risk of infection with SARS-CoV-2 and death due to COVID-19 in people older than 60 years in Argentina: a test-negative, case-control, and retrospective longitudinal study. *Lancet.* 2022;399(10331):1254–1264.
- 20 Al Kaabi N, Zhang Y, Xia S, et al. Effect of 2 inactivated SARS-CoV-2 vaccines on symptomatic COVID-19 infection in adults: a randomized clinical trial. *JAMA.* 2021;326(1):35–45.
- 21 Wu D, Zhang Y, Tang L, et al. Effectiveness of inactivated COVID-19 vaccines against symptomatic, pneumonia, and severe disease caused by the delta variant: real world study and evidence - China, 2021. *China CDC Wkly.* 2022;4(4):57–65.
- 22 Li XN, Huang Y, Wang W, et al. Effectiveness of inactivated SARS-CoV-2 vaccines against the Delta variant infection in Guangzhou: a test-negative case-control real-world study. *Emerg Microbes Infect.* 2021;10(1):1751–1759.
- 23 Arregocés-Castillo L, Fernández-Niño J, Rojas-Botero M, et al. Effectiveness of COVID-19 vaccines in older adults in Colombia: a retrospective, population-based study of the ESPERANZA cohort. *Lancet Healthy Longev.* 2022;3(4):e242–e252.
- 24 Vokó Z, Kiss Z, Surján G, et al. Nationwide effectiveness of five SARS-CoV-2 vaccines in Hungary—the HUN-VE study. *Clin Microbiol Infect.* 2022;28(3):398–404.
- 25 Al Kaabi N, Oulhaj A, Ganesan S, et al. Effectiveness of BBIBP-CorV vaccine against severe outcomes of COVID-19 in Abu Dhabi, United Arab Emirates. *Nat Commun.* 2022;13(1):3215.
- 26 Ismail AlHosani F, Eduardo Stanciole A, Aden B, et al. Impact of the Sinopharm's BBIBP-CorV vaccine in preventing hospital admissions and death in infected vaccinees: results from a retrospective study in the emirate of Abu Dhabi, United Arab Emirates (UAE). *Vaccine.* 2022;40(13):2003–2010.
- 27 Khairullin B, Zakarya K, Orynbayev M, et al. Efficacy and safety of an inactivated whole-virion vaccine against COVID-19, QazCovid-in<sup>®</sup>, in healthy adults: a multicentre, randomised, single-blind, placebo-controlled phase 3 clinical trial with a 6-month follow-up. *eClinicalMedicine.* 2022;50:101526.
- 28 Ella R, Reddy S, Blackwelder W, et al. Efficacy, safety, and lot-to-lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): interim results of a randomised, double-blind, controlled, phase 3 trial. *Lancet.* 2021;398(10317):2173–2184.
- 29 Sritipsukho P, Khawcharoenporn T, Siribumrungwong B, et al. Comparing real-life effectiveness of various COVID-19 vaccine regimens during the delta variant-dominant pandemic: a test-negative case-control study. *Emerg Microbes Infect.* 2022;11(1):585–592.
- 30 Nadeem I, Ata Ul Munamm S, Rasool M, et al. Safety and efficacy of Sinopharm vaccine (BBIBP-CorV) in elderly population of Faisalabad district of Pakistan. *Postgrad Med J.* 2022;postgradmedj-2022.
- 31 Cerqueira-Silva T, Andrews JR, Boaventura VS, et al. Effectiveness of CoronaVac, ChAdOx1 nCoV-19, BNT162b2, and Ad26.COV2.S among individuals with previous SARS-CoV-2 infection in Brazil: a test-negative, case-control study. *Lancet Infect Dis.* 2022;22(6):791–801.
- 32 Cerqueira-Silva T, Katikireddi SV, de Araujo Oliveira V, et al. Vaccine effectiveness of heterologous CoronaVac plus BNT162b2 in Brazil. *Nat Med.* 2022;28(4):838–843.
- 33 Can G, Acar HC, Aydin SN, et al. Waning effectiveness of CoronaVac in real life: a retrospective cohort study in health care workers. *Vaccine.* 2022;40(18):2574–2579.
- 34 Hitchings MDT, Ranzani OT, Torres MSS, et al. Effectiveness of CoronaVac among healthcare workers in the setting of high SARS-CoV-2 Gamma variant transmission in Manaus, Brazil: a test-negative case-control study. *Lancet Reg Health Am.* 2021;1:100025.
- 35 Ranzani OT, Hitchings MDT, Dorion M, et al. Effectiveness of the CoronaVac vaccine in older adults during a gamma variant associated epidemic of Covid-19 in Brazil: test negative case-control study. *BMJ.* 2021;374:n2015.
- 36 Marra AR, Miraglia JL, Malheiros DT, et al. Effectiveness of two COVID-19 vaccines (viral vector and inactivated viral vaccine) against SARS-CoV-2 infection in a cohort of healthcare workers. *Infect Control Hosp Epidemiol.* 2022;44(1):75–81.
- 37 González S, Olszevicki S, Gaiano A, et al. Effectiveness of BBIBP-CorV, BNT162b2 and mRNA-1273 vaccines against hospitalisations among children and adolescents during the Omicron outbreak in Argentina: a retrospective cohort study. *Lancet Reg Health Am.* 2022;13.
- 38 Jara A, Undurraga EA, González C, et al. Effectiveness of an inactivated SARS-CoV-2 vaccine in Chile. *N Engl J Med.* 2021;385(10):875–884.
- 39 Tanriover MD, Doğanay HL, Akova M, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. *Lancet.* 2021;398(10296):213–222.
- 40 Fadlyana E, Rusmil K, Tarigan R, et al. A phase III, observer-blind, randomized, placebo-controlled study of the efficacy, safety, and immunogenicity of SARS-CoV-2 inactivated vaccine in healthy adults aged 18–59 years: an interim analysis in Indonesia. *Vaccine.* 2021;39(44):6520–6528.
- 41 Suah JL, Tok PSK, Ong SM, et al. PICK-ing Malaysia's epidemic apart: effectiveness of a diverse COVID-19 vaccine portfolio. *Vaccines.* 2021;9(12):1381.
- 42 Jara A, Undurraga EA, Zubizarreta JR, et al. Effectiveness of CoronaVac in children 3–5 years of age during the SARS-CoV-2 Omicron outbreak in Chile. *Nat Med.* 2022;28(7):1377–1380.
- 43 Mirahmadzadeh A, Heiran A, Bagheri Lankarani K, et al. Effectiveness of coronavirus disease 2019 vaccines in preventing infection, hospital admission, and death: a historical cohort study using Iranian registration data during vaccination program. *Open Forum Infect Dis.* 2022;9(6):ofac177.
- 44 Behera P, Singh AK, Subba SH, et al. Effectiveness of COVID-19 vaccine (Covaxin) against breakthrough SARS-CoV-2 infection in India. *Hum Vaccin Immunother.* 2022;18(1):2034456.
- 45 Petrović V, Vuković V, Marković M, Ristić M. Early effectiveness of four SARS-CoV-2 vaccines in preventing COVID-19 among adults Aged ≥60 Years in Vojvodina, Serbia. *Vaccines.* 2022;10(3):389.
- 46 World Health Organization. Vaccine efficacy, effectiveness and protection [Internet]. Available from: <https://www.who.int/news-room/feature-stories/detail/vaccine-efficacy-effectiveness-and-protection>; 2021. Accessed August 2, 2022.
- 47 Suah JL, Husin M, Tok PSK, et al. Waning COVID-19 vaccine effectiveness for BNT162b2 and CoronaVac in Malaysia: an observational study. *Int J Infect Dis.* 2022;119:69–76.
- 48 Collier DA, Ferreira IATM, Kotagiri P, et al. Age-related immune response heterogeneity to SARS-CoV-2 vaccine BNT162b2. *Nature.* 2021;596(7872):417–422.
- 49 Güzel E, Çelikkol A, Erdal B, Sedef N. Immunogenicity after CoronaVac vaccination. *Rev Assoc Med Bras.* 2021;67(10):1403–1408.
- 50 Greish K, Alawadhi A, Jaradat A, et al. Safety and Immunogenicity of COVID-19 BBIBP-CorV vaccine in children 3–12 years old. *Vaccines.* 2022;10(4):586.
- 51 Mallapaty S. China's COVID vaccines have been crucial — now immunity is waning. *Nature.* 2021;598(7881):398–399. Available from: <https://www.nature.com/articles/d41586-021-02796-w>. Accessed August 2, 2022.
- 52 Tancredi S, Anker D, Rosella L, Chiolerio A. Elimination of Covid-19: beware of surveillance bias. *BMJ.* 2021;374:n2126.
- 53 Chirico F, Teixeira da Silva JA, Magnavita N. "Questionable" peer review in the publishing pandemic during the time of COVID-19: implications for policy makers and stakeholders. *Croat Med J.* 2020;61(3):300–301.
- 54 McMenamin ME, Nealon J, Lin Y, et al. Vaccine effectiveness of one, two, and three doses of BNT162b2 and CoronaVac against COVID-19 in Hong Kong: a population-based observational study. *Lancet Infect Dis.* 2022;22(10):1435–1443. [https://doi.org/10.1016/S1473-3099\(22\)00345-0](https://doi.org/10.1016/S1473-3099(22)00345-0). Erratum in: *Lancet Infect Dis.* 2022 Sep;22(9):e239.
- 55 Yan VKC, Wan EYF, Ye X, et al. Effectiveness of BNT162b2 and CoronaVac vaccinations against mortality and severe complications after SARS-CoV-2 Omicron BA.2 infection: a case-control study. *Emerg Microbes Infect.* 2022;11(1):2304–2314. <https://doi.org/10.1080/22221751.2022.2114854>.