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ASSESSING THE EFFECTIVENESS AND SAFETY OF COVID- 19 VACCINES

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Abstract
While the coronavirus was a global health crisis, it also generated enormous socio-economic challenges such as trading. Buying and selling, socio-economic meltdown, health sector breakdown. Poor housing facilities. Poverty, unemployment, low income, inequality, and epileptic power supply. Amongst others, in developing countries like Nigeria. This thesis adopts a systemic approach, using a random-effects meta- analysis framework to aggregate findings from peer-reviewed studies conducted between 2021 and 2024 to account for between-study heterogeneity.
The pooled overall effect size (exp (b)) was I.658 (95% CI: 1.407-1.953, P<0.0001) indicating a statistically vaccine effectiveness across the studies. Substantial heterogeneity wvas observed among the studies, as indicated by an [² = 96.8%, which suggests variability in study populations, vaccines types. or methodologies.

1. INTRODUCTION

The global population is facing unimagined situations caused by the coronavirus (COVID-19) pandemic, which was reported in Wuhan, one of the most populous cities in China, in December 2019 (Forster et al., 2020; World Health Organization, 2020; Yang et al., 2020). The virus spread internationally within 1 month of the first identification and was transmitted via close human-to-human contact (Huang et al., 2020). The outbreak of the virus was declared a public health emergency of international concern and a pandemic on January 30, 2020, and March 11, 2020, respectively, by the World Health Organization (Farzanegan et al., 2020).

The Coronavirus pandemic was caused by a novel coronavirus (SARS-Cov-2) that is believed to have crossed from bats to humans for the first time. COVID-19 is an infectious disease of the respiratory system of humans and animals, and the virus can be transmitted through facial openings, including the mouth, nostrils, and possibly eyes (Hussaini Majiya et al).

The virus, which was renamed Coronavirus Disease in the year 2019 or COVID-19 (it was formerly known as the 2019-nCoV acute respiratory disease) by the World Health Organization, has infected approximately 76,936

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people in mainland China, with additional 2,051 cases of the virus from approximately 30 other countries. Just looking at the number of instances of total coronavirus and the figures of the affected countries does not tell the whole story of 118,142 total cases with 4,264 deaths accounted worldwide in 114 countries, which signifies that more than 90 per cent of the total cases of the virus are in just 4 countries, and two of those of China and the Republic of Korea have significantly declining epidemics, 81 countries have not reported any cases of the virus, and the 57 other countries have revealed 10 cases of the virus or less.

The WHO has been evaluating this epidemic around the clock, and they are extremely worried both by the increasing spread stage and harshness and by the increasing levels of inaction. On 10th March 2020, the WHO made it clear that COVID-19 can be described as a global pandemic, and a pandemic is not a word to use evenly or carelessly but a word that, if misused, can cause unreasonable fear or unfair acceptance that the fight against the virus is over, leading to needless suffering and death. Describing the situation as a pandemic does not change an organization's consideration of the danger posed by this virus and it does not change what organizations and countries should do. Figure 2 shows the total number of deaths worldwide caused by coronavirus disease from 20th January to 10th March 2020.

Nigeria received her shipped-in share of the novel coronavirus through an Italian consultant who arrived in Nigeria on February 27, 2020, and reported by the Nigerian Center for Disease Control (NCDC) on the 28th January 2020, being the first reported case of COVID-19 in sub- Saharan Africa (Ebenso & Out, 2020; Nigeria Center for Disease Control, 2020a, b, c). As the World Health Organization predicted, the rate at which COVID-19 is spreading in Nigeria is generating serious health concerns from the weak healthcare system (National Bureau of Statistics, 2015; WHO, 2016; Oyekale, 2017). The inadequacies and challenges that exist across the health system, such as the inadequate supply of human and material resources, and low belief (Okechukwu et al., 2020; Onalu et al., 2020), probably because the Nigerian system in the new healthcare system, poor attitude of health practitioners, non-employment of social workers in Primary Health Centers, zero levels of people's involvement, and inefficient service provision prove a very dangerous threat (Krumkamp et al., 2013; Okwaraji et al., 2012; Oyekale, 2017; Uzochukwu et al., 2018; Okoye, 2019). These issues, therefore, raise the question of the reality and ability of the Nigerian healthcare system to contain a full-blown coronavirus outbreak in the country, especially in the rural areas. Currently, the containment of COVID-19 in Nigeria is facing many logistic, administrative, and social barriers, such as few testing and isolation centers, lack of medical equipment and personnel, especially in the area of infectious diseases, and both noninvolvement of social workers and low motivation of medical personnel (Anyika, 2014; Ibama & Dennis, 2016; Jaeger et al., 2018; Obansa & Orimisan, 2013; Titus et al., 2015). This, therefore, confirms the current reality in Nigeria, where the workforce (medical/ nonmedical), medical products, medical structures, technologies and information available are all insufficient to achieve maximum health coverage and quality delivery, respectively (Eboreime et al., 2015; Oyekale, 2017; Uzochukwu et al., 2018). The fight against COVID-19 in Nigeria is also faced with challenges of low public compliance with social distancing, wearing face masks, and constant handwashing, probably because social workers were not involved in the required public education and awareness creation. Some traditional practitioners and pastors in Nigeria believe in supernatural and preternatural forces when approaching this public health issue (Benedict, 2014; Ibeneme et al., 2017; Jaeger et al., 2018). Social workers in Nigeria are not part of the fight against the pandemic as obtains in some other parts of the world, such as China, South Africa, New Zealand, and Italy. Unfortunately, the majority of social workers in Nigeria appear not to be aware of the roles they need to play during the pandemic (the Nnama government did not accord the needed relevance for their roles. The lack of such welfare services for vulnerable people, households, and poor individuals during the COVID-19 outbreak

in Nigeria caused severe pain and economic hardship for households and poor individuals. It is against this backdrop that this chapter draws attention to the indispensable role of social workers in the period of a public health emergency. In the same vein, social workers' responsibilities in the areas of social welfare provision and care for poor and vulnerable people are relevant (Onalu et al.)

2. Statement of the Problem

Due to the complex nature of the country (large population size), there was a poor healthcare system manned by inadequate diagnostics and isolation centers, there was not enough data to present to a layman the numbers of affected individuals or even the ages at which the virus affected the most as the case may be and corruption. Fighting this public health crisis is therefore filled with numerous challenges including; poor preparedness and response plans. Therefore, this study aimed to conduct a meta-analysis on the effectiveness of COVID-19 vaccines. The effectiveness of vaccines is measured by how well the shot works when administered to people outside clinical trials.

3. Aim of the Study

To assess the effectiveness and safety of COVID-19 vaccines using a random-effects model.

Objectives of the Study

i. To conduct a thorough review and analysis of the current literature on the effectiveness and safety of COVID-19 vaccines.

ii. The random effects model was used to calculate pooled effect sizes, accounting for both within- and between-study variability, and study heterogeneity was assessed using Cochran's Q and I^2 statistics.

iii. To perform sensitivity analyses to confirm the reliability of the results and thoroughly interpret the pooled effect sizes and their confidence intervals, offering practical and actionable recommendations for enhancing COVID-19 treatment approaches.

4. Definition of Terms and Acronyms

Effectiveness: Effectiveness refers to the real-world performance of COVID-19 vaccines in preventing infection, reducing disease severity, and lowering hospitalization and mortality rates. Unlike efficacy, which is measured under controlled clinical trial conditions, effectiveness is assessed in broader populations with varying health conditions and exposure risks.

COVID-19: Coronavirus Disease 2019 (COVID-19) is an infectious respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It presents with a range of symptoms, from mild flu-like manifestations to severe pneumonia, multi-organ failure, and death, particularly in high-risk individuals.

Vaccination: The administration of a vaccine to stimulate the immune system to recognize and combat pathogens, in this case, SARS-CoV-2. This strategy aims to prevent severe disease, reduce transmission, and contribute to long-term immunity within the population.

Herd Immunity: Herd immunity (or population immunity) occurs when a significant portion of a population develops immunity to a disease—either through vaccination or previous infection—thereby reducing its spread and protecting unvaccinated individuals. The threshold for herd immunity against COVID-19 depends on several factors, such as vaccine effectiveness and variant transmissibility.

Vaccine Hesitancy: Vaccine hesitancy is defined by the World Health Organization as a "delay in acceptance or refusal of vaccination despite the availability of vaccination services." It is influenced by factors such as misinformation, distrust of public health authorities, religious or cultural beliefs, and concerns about vaccine safety.

Booster Dose: A booster dose is an additional vaccine dose administered after the primary vaccination series to enhance or restore immunity. Booster shots are particularly important for maintaining protection against emerging SARS-CoV-2 variants and ensuring long-term immunity.

Breakthrough Infection: A breakthrough infection occurs when a fully vaccinated individual contract COVID-19. Although such infections can occur, they are generally associated with milder symptoms and a significantly lower risk of severe outcomes compared with unvaccinated individuals.

Variants of Concern (VOCs): Variants of Concern (VOCs) are mutated strains of SARS-CoV-2 virus that exhibit increased transmissibility, altered disease severity, or potential resistance to immunity acquired through vaccination or prior infection. Examples include the Delta and Omicron variants, which have influenced vaccine effectiveness and public health strategies.

Adverse Effects: Adverse effects refer to unintended reactions following vaccination. These range from mild side effects (e.g., pain at the injection site, fever, fatigue) to rare but serious complications (e.g., myocarditis, anaphylaxis). The benefits of vaccination typically outweigh the risks of such effects.

Vaccine Coverage Rate: The vaccine coverage rate is the proportion of a population that has received one or more doses of a COVID-19 vaccine. This metric is essential for assessing the progress of immunization campaigns and predicting population-level immunity.

Acronyms

COVID-19 – Coronavirus Disease 2019

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

WHO, World Health Organization

CDC–Centers for Disease Control and Prevention

FDA: Food and Drug Administration

EMA: European Medicines Agency

NIH, National Institutes of Health

MOH, Ministry of Health (varies by country)

PHC: primary health care

Vaccine-Specific Acronyms

MRNA–Messenger Ribonucleic Acid (used in vaccines like Pfizer and Moderna)

DNA–Deoxyribonucleic Acid (used in some vaccine platforms)

VE – Vaccine Effectiveness

VEP–Vaccine Efficacy for Protection against Infection

VESP–Vaccine Efficacy for Protection against Symptomatic Disease

VES–Vaccine Efficacy for Severe Disease Protection

TTS: Thrombosis with Thrombocytopenia Syndrome (a rare side effect of some COVID-19 vaccines)

Vaccine Names and Types

BNT162b2: Pfizer-BioNTech COVID-19 Vaccine

MRNA-1273 – Moderna COVID-19 Vaccine

AZD1222–AstraZeneca COVID-19 Vaccine

J&J (Ad26.COV2.S) – Johnson & Johnson COVID-19 Vaccine

BBIBP-CorV – Sinopharm COVID-19 Vaccine

CoronaVac–Sinovac COVID-19 Vaccine

NVX-CoV2373 – Novavax COVID-19 Vaccine

Covaxin (BBV152) – Bharat Biotech COVID-19 Vaccine
Sputnik V: Russian COVID-19 Vaccine

5. Research Design

This meta-analysis employed a quantitative research design to evaluate the impact of coronavirus vaccines in selected hospitals within Abuja. Meta-analysis, a statistical technique that integrates the findings of multiple studies, is particularly suitable for synthesizing research results to derive a comprehensive understanding of the effectiveness of vaccines. This method allows for the aggregation of data from diverse studies, enhancing the statistical power and providing more robust conclusions than individual studies (Borenstein et al., 2009).

6. Population, Sample, and Sampling Techniques

The study population comprised research articles, reports, and case studies published between 2020 and 2023, focusing on the effectiveness of COVID-19 vaccines administered to hospitals in Abuja. The sample includes studies sourced from academic databases such as PubMed, Google Scholar, and institutional repositories.

Sampling was conducted using purposive sampling techniques to ensure the selection of studies that meet specific inclusion criteria:

1. Studies must be conducted in Abuja.
2. They must evaluate the impact of COVID-19 vaccines.
3. They should provide quantitative data on vaccine effectiveness, adverse effects, and vaccination coverage.

This approach ensures that only relevant and high-quality studies are included, thereby enhancing the validity of the meta-analysis (Patton, 2015).

7. Method of Data Collection

Data collection was carried out through a systematic review of relevant literature. The process began with an extensive search using specific keywords such as “COVID-19 vaccine,” “effectiveness,” and “impact” across reputable scientific databases. Initial screening involved evaluating the titles and abstracts of the retrieved studies to eliminate those that did not meet the inclusion criteria or were deemed irrelevant to the research focus.

Subsequently, full-text reviews were conducted on the remaining articles to extract relevant data. Key information obtained included study design, sample size, vaccine type, reported effectiveness, and any noted adverse effects. To maintain consistency and accuracy, a standardized data extraction form was used. This form was designed to capture the following variables:

Study Identification: Author(s), year of publication
Population Characteristics: Age distribution, gender, and presence of comorbidities
Vaccine Type: Pfizer-BioNTech, Moderna, AstraZeneca, and others
Measured Outcomes: Infection, hospitalization, and mortality rates
Statistical Measures: Odds ratios (OR), relative risks (RR), and confidence intervals (CI)

This structured approach ensured a reliable synthesis of findings across studies and facilitated accurate comparisons of vaccine effectiveness and associated health outcomes.

8. Data Analysis Technique

The analysis was conducted using statistical software such as Comprehensive Meta-Analysis (CMA) or RevMan. The primary technique involved calculating pooled effect sizes using a random-effects model, which accounts for the variability among studies (Higgins et al., 2011). Heterogeneity among studies was assessed using the I^2 statistic, with values above 50% indicating substantial heterogeneity (Higgins & Thompson, 2002).

Sensitivity analyses were performed to examine the robustness of the results by excluding studies with high risk of bias or extreme effect sizes. Publication bias was assessed using funnel plots and Egger's test (Egger et al., 1997).

Random Effects Meta-Analysis

Naturally, in a real meta-analysis, we begin with the observed effects and attempt to estimate the population impact, as opposed to starting with the population effect and making projections about the observed effects. If otherwise stated, our objective is to estimate the overall mean μ, using the Yi collection. We computed a weighted mean, where the weight allocated to each research equals the inverse of that study's variance, in order to produce the most accurate estimate of the overall mean (to minimize the variance).

Since the study's overall variance is the sum of these two values, we must know both the within-study variance and τ^2 in order to compute a study's variance under the random-effects model. There are formulas for calculating within-study variation.

Since the study's overall variance is the sum of these two values, we must know both the within-study variance and τ^2 in order to compute a study's variance under the random-effects model. There are formulas for calculating within-study variation. A method for estimating the between-study variance is also provided.

Estimating Tau-Squared

The parameter τ^2 (tau-squared) is the between-study variance (the variance of the effect size parameters across the population of studies). In other words, if we somehow knew the true effect size for each study and computed the variance of these effect sizes (across an infinite number of studies), this variance would be τ^2. One method for estimating τ^2 is the moments method (or the DerSimonian and Laird) method, as follows. However, before that, we consider the following assumptions;

(1) fixed-effect model assumption

- Each study *(i) provides* an estimate Yi of the true effect size θ.
- The observed effect Yi follows a normal distribution: $Yi \sim N(\theta i, \sigma_i^2)$
- σ_i^2 is the within-study variance

(2) Random-effects model

- The random effects model assumes that true effect sizes θi vary across studies.
- This variation is modeled as $\theta i \sim N(\theta, \tau^2)$, where τ^2 is the between-study variance.
- The observed effect size Yi is then modeled as $Yi \sim N(\theta, \sigma_i^2 + \tau^2)$

(3) Weighted mean effect size (Random effects)

- In the random-effects model, the overall size $\hat{\theta}$ is a weighted mean of the study-specific effect size Yi.

$$\hat{\theta} = \frac{\sum_{i=1}^{k} wiYi}{\sum_{i=1}^{k} wi} \qquad (3.1)$$

Here the weights wi are defined as follows:

$$wi = \frac{1}{\sigma i2 + \tau 2}$$

DerSimonian Laird Estimator τ^2

$$T^2 = \frac{Q - df}{C}, \qquad (3.2)$$

Where

$$Q = \sum_{i=1}^{k} W_i Y_i^2 - \frac{\left(\sum_{i=1}^{k} W_i Y_i\right)^2}{\sum_{i=1}^{k} W_i}, \qquad df = k\ \ 1, \tag{3.3}$$

where; k is the number of studies, and

$$C = \sum W_i - \frac{\sum W_i^2}{\sum W_i}. \tag{3.4}$$

Tau-squared (τ^2) is a measure of heterogeneity in meta-analysis, representing the variance of true effect sizes across different studies. Here's the derivation of the formula for τ^2 using the DerSimonian and Laird method, which is commonly used in random-effects meta-analysis.

Estimating Mean Effect Size

In the fixed-effect analysis, each study was weighted by the inverse of its variance. In the random-effects analysis, each study is also weighted by the inverse of its variance. The difference is that the variance now includes the original (within- studies) variance plus the estimate of the between-studies variance, T^2. In keeping with the book's convention, we use τ^2 to refer to the parameter and T^2 to refer to the sample estimate of that parameter.

To highlight the parallel between the formulas here (random effects) and those in the previous chapter (fixed effect), we use the same notations but add an asterisk (*) to represent the random-effects version. Under the random-effects model, the weight assigned to each study was

$$W_i^* = \frac{1}{V_{Y_i}^*}, \tag{3.5}$$

Where V^*_{Yi} is the within-study variance for study *i* plus the between-study variance, T^2. That is,

$$V_{Y_i}^* = V_{Y_i} + T^2. \tag{3.6}$$

The weighted mean M* is then computed as follows:

$$M^* = \frac{\sum_{i=1}^{k} W_i^* Y_i}{\sum_{i=1}^{k} W_i^*}, \tag{3.7}$$

That is, the sum of the products (effect size multiplied by weight) divided by the sum of the weights.

The variance of the summary effect is estimated as the reciprocal of the sum of the weights as follows:

$$V_{M^*} = \frac{1}{\sum_{i=1}^{k} W_i^*}, \tag{3.8}$$

And the estimated standard error of the summary effect is then the square root of the variance as follows:

$$SE_{M^*} = \sqrt{V_{M^*}}. \tag{3.9}$$

the 95% lower and upper limits for the summary effect were computed as follows:

$$LL_{M^*} = M^* — 1{:}96 \times SE_{M^*}; \tag{3.10}$$

And

$$UL_{M^*} = M^* + 1{:}96 \times SE_{M^*}: \tag{3.11}$$

Finally, a Z-value to test the null hypothesis that the mean effect μ is zero was computed as follows:

Using $$Z^* = \frac{M^*}{SE_{M^*}}. \tag{3.12}$$

For a one-tailed test, the p-value was calculated as follows:

$$p^* = 1 - \Phi(\pm|Z^*|), \quad (3.13)$$

Where we choose '+' if the difference is in the expected direction or '–' otherwise, and for a two-tailed test by

$$p^* = 2[1 - (\Phi(|Z^*|))], \quad (3.14)$$

Where Φ(Z*) denotes the standard normal cumulative distribution. This function is presented in many introductory statistics books and is implemented in Excel as follows:

=NORMSDIST (Z*).

A. Assessment of Heterogeneity: Heterogeneity among studies was assessed using the I-squared (I^2) statistic, which quantifies the proportion of total variation across studies due to heterogeneity rather than chance. I^2 values greater than 50% indicated substantial heterogeneity (Higgins et al., 2003). Subgroup analyses were conducted to explore potential sources of heterogeneity, such as study location, study design, and drug resistance assessment methods.

C. **Subgroup Analyses:** Subgroup analyses were performed to investigate potential sources of heterogeneity and explore variations in drug resistance prevalence across different subgroups of studies. Subgroup analyses were conducted based on factors such as study location (e.g., geographical region, endemicity), study design (e.g., cross-sectional studies, longitudinal studies), and drug resistance assessment methods (e.g., molecular methods, phenotypic methods).

D. **Sensitivity Analyses:** Sensitivity analyses were conducted to assess the robustness of the findings to variations in study quality, methodology, and inclusion criteria. Sensitivity analyses involved excluding studies with high risk of bias or low methodological quality and assessed the impact of outliers on the overall effect size estimates.

E. Publication Bias Assessment: Publication bias, which arises from the selective publication of studies with positive or significant results, was assessed using funnel plots and Egger's regression test (Egger et al., 1997). Funnel plot asymmetry and significant Egger's test results indicated potential publication bias. Adjustments such as the trim-and-fill method were applied to address publication bias and provide adjusted effect size estimates.

The pooled prevalence of drug resistance in malaria parasites was estimated using random-effects meta-analysis models. The DerSimonian-Laird method was used to calculate the overall effect size, along with 95% confidence intervals. Heterogeneity among studies was assessed using the I-squared statistic, with values greater than 50% indicating substantial heterogeneity. Subgroup analyses were conducted to explore potential sources of heterogeneity, such as study location, study design, and drug resistance assessment methods. Sensitivity analyses were performed to assess the robustness of the findings to variations in study quality and methodology.

F. Quality Assessment: Quality assessment is essential in meta-analysis to evaluate the risk of bias and methodological quality of included studies, thereby ensuring the reliability and validity of the synthesized evidence. This section elaborates on the quality assessment process, including the tools used, the evaluation criteria, and the implications for data synthesis.

Tools Used: Quality assessment was conducted using established tools such as the Newcastle-Ottawa Scale (NOS) for observational studies (Wells et al., 2020) or the Cochrane Risk of Bias tool for randomized controlled trials (Sterne et al., 2019). These tools provide structured criteria for assessing various aspects of study quality, including selection, performance, detection, attrition, and reporting bias.

9. Justification of Methods

The chosen research design and methods are justified based on their ability to provide a rigorous and comprehensive evaluation of the impact of COVID-19 vaccines. Meta-analysis is particularly effective for synthesizing results across different studies, providing higher statistical power and more generalized findings (Borenstein et al., 2009).

Purposive sampling ensures that only the most relevant studies are included, enhancing the applicability of the findings to the target population within Abuja. The systematic data collection process ensures thoroughness and minimizes bias, and the statistical techniques used for data analysis are well-established and widely accepted in the field of epidemiology (Higgins et al., 2011).

These methods collectively enhance the reliability and validity of the study, providing valuable insights into the effectiveness of COVID-19 vaccines in the selected hospitals within Abuja.

10. Data Presentation

S/N	Author	Risk ratio	Lower Con. interval	Upper Con. The interval	Confidence Interval
1	Ali Pormohammad et al. (2021)	0.837	0.67	0.93	0.95
2	Haoyue Cheng et al. (2021)	0.17	0.09	0.32	0.95
3	Marharyta Sobczak et al. (2022)	0.36	0.25	0.53	0.95
4	Yu-Jing Fan et al. (2021)	0.17	0.07	0.4	0.95
5	Ainsley Ryan et al. (2022)	0.4	0.32	0.5	0.95
6	Carolina GrañaLina et al. (2022)	0.25	0.09	0.67	0.95
7	Ikhwan Rinaldi et al. (2022)	0.6	0.5	0.71	0.95
8	Rashidul Alam et al. (2021)	0.15	0.07	0.31	0.95
9	Yuxuan Du et al. (2022)	1.4	1.04	1.9	0.95
10	Jun Zhang et al. (2023)	0.76	0.73	0.78	0.95
11	Sushma Kavikondala et al. (2024)	0.72	0.64	0.8	0.95

This study systematically reviewed and conducted a meta-analysis of 11 studies assessing the effectiveness and safety of COVID-19 vaccines worldwide. The extracted data were synthesized and analyzed using a random-effects model to account for between-study heterogeneity. The following results were obtained:

- The pooled overall effect size (exp(b)) was 1.658 (95% CI: 1.407 – 1.953), indicating statistically significant vaccine effectiveness across the studies.
- Forest plot analysis demonstrated consistent vaccine effectiveness across individual studies, with some variation in the magnitude of the effect sizes.
- Heterogeneity analysis revealed substantial variation between studies ($I^2 = 96.8\%$), suggesting variability in study populations, vaccine types, and methodologies.

Subgroup and sensitivity analyses were conducted to investigate the robustness and stability of the results. The findings are summarized as follows:

1. Forest Plot

   The forest plot (Figure X) revealed that all included studies had a positive effect size (greater than 1), confirming the effectiveness of COVID-19 vaccines. The study weights ranged from 5.94% to 10.04%, with Jun Zhang et al. (2023) contributing the highest weight.

2. Funnel Plot for Publication Bias

The funnel plot indicates asymmetry, suggesting the possibility of publication bias. This asymmetry may be

attributed to the inclusion of smaller studies with larger effect sizes. However, the presence of bias does not negate the robustness of the findings, as demonstrated by the sensitivity analyses.

3. Subgroup Analysis

The subgroup analysis revealed differences in effect sizes between two groups:

a) Subgroup 0 (9 studies) had a pooled estimate of 1.562 (95% CI: 1.307–1.868, I^2 =93.3%).

b) Subgroup 1 (2 studies) had a pooled estimate of 2.131 (95% CI: 2.080 – 2.182, I^2 = 0.0%). The low heterogeneity in Subgroup 1 indicates greater consistency in the results of these studies.

4. Sensitivity Analyses

Both manual and leave-one-out sensitivity analyses demonstrated the robustness of the findings. When individual studies were omitted, the pooled effect sizes ranged from 1.613 to 1.999, indicating no drastic changes in the overall effect size.

11. Meta-Analysis Results:

Using the random-effects model, the aggregate data demonstrated the significant effectiveness of COVID-19 vaccines.

The DerSimonian-Laird estimate of tau^2 captured between-study variance, ensuring robust analysis.

Studies included: 11

Meta-analysis pooling of aggregate data using the random-effects inverse-variance model with DerSimonian-Laird estimate of tau^2

author	exp(b)	[95% Conf.	Interval]	% Weight
Ali Pormohammad et al. (2021)	2.309	1.958	2.529	9.48
Haoyue Cheng et al. (2021)	1.185	1.094	1.377	9.59
Marharyta Sobczak et al. (2022)	1.433	1.284	1.699	9.37
Yu-Jing Fan et al. (2021)	1.185	1.073	1.492	9.13
Ainsley Ryan et al. (2022)	1.492	1.377	1.649	9.76
Carolina GrañaLina et al. (2022	1.284	1.094	1.954	7.65
Ikhwan Rinaldi et al. (2022)	1.822	1.649	2.034	9.66
Rashidul Alam et al. (2021)	1.162	1.073	1.363	9.55
Yuxuan Du et al. (2022)	4.055	2.829	6.686	5.94
Jun Zhang et al. (2023)	2.138	2.075	2.181	10.04
Sushma Kavikondala et al. (2024)	2.054	1.896	2.226	9.83
Overall, DL	1.658	1.407	1.953	100.00

Test of overall effect = 1: z = 6.047, p = 0.000

Heterogeneity measures calculated from the data with Conf. Intervals based on the gamma (random-effects) distribution for Q

Measure	Value	df	p-value
Cochran's Q	311.80	10	0.000
		[95% Conf.	Interval]
H	5.584	1.849	9.430
I^2 (%)	96.8%	70.7%	98.9%

H = relative excess in Cochran's Q over its degrees of freedom

I^2 = (96.8%) proportion of total variation in effect estimate due to between-study heterogeneity (based on Q=311.80)

Heterogeneity variance estimates

Method	tau^2
DL	0.0695

Effect Size (Exp(b)): The reported effect sizes represent the vaccine's effectiveness or relative safety, where exp(b) > 1 suggests beneficial effects. The overall effect size was 1.658 (95% CI: 1.407–1.953), indicating that COVID-19 vaccines are overall effective and safe. The confidence interval does not include 1, which indicates statistical significance. Test of overall effect (z = 6.047, p = 0.000): This strongly supports that the effectiveness/safety of vaccines is significantly different from a null effect.

Individual Studies: Each study contributes a specific effect size with a 95% confidence interval and weight in the meta-analysis. For example:

Yuan Du et al. (2022): This study reports the largest effect size exp(b)=4.055 (95% CI: 2.829–6.686), suggesting highly significant benefits. Ali Pormohammad et al. (2021): Has exp(b) = 2.309 (95% CI: 1.958–2.529), also indicating significant benefit. Studies with narrower confidence intervals, such as Jun Zhang et al. (2023) (exp(b) = 2.138, CI: 2.075 – 2.181), provide more precise estimates. Weights vary between studies (e.g., Jun Zhang et al. = 10.04%, Yuxuan Du et al. = 5.94%), depending on sample size, variance, and study design.

12. Heterogeneity

Cochran's Q (Q = 311.80, p = 0.000): This test indicates significant heterogeneity among the studies ($p < 0.05$).

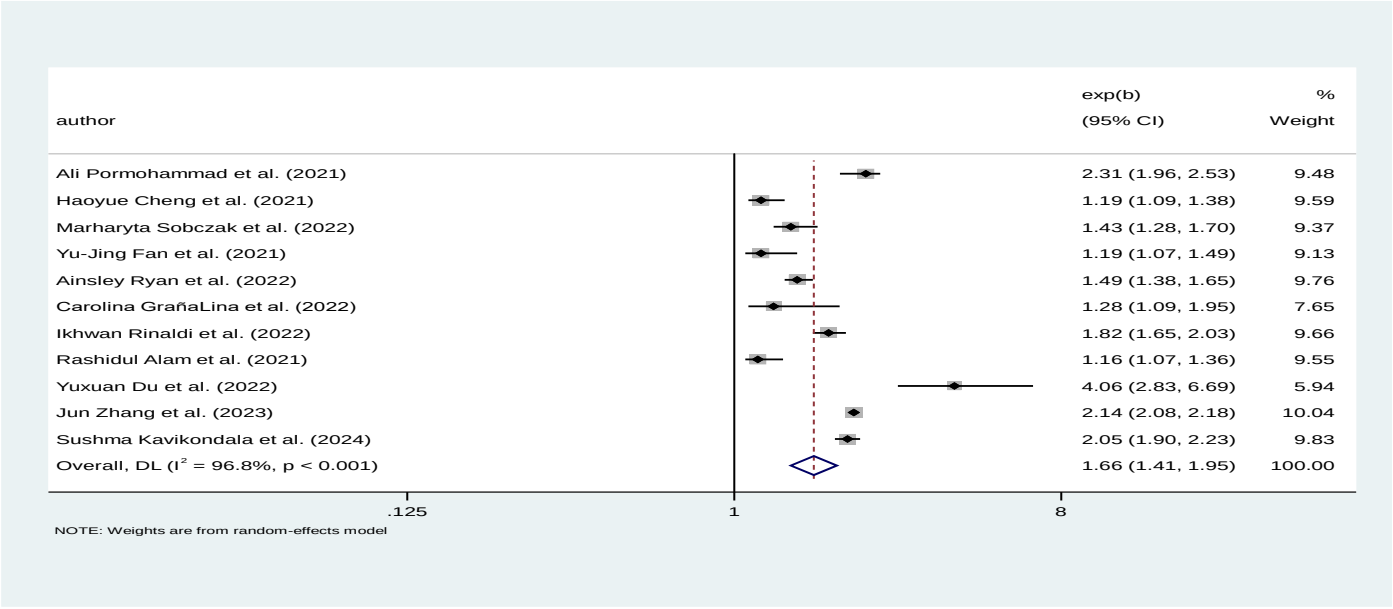
H-statistic (H = 5.584, 95% CI: 1.849–9.430): Shows relative excess variability.

I^2 = 96.8% (95% CI: 70.7%–98.9%): This indicates that 96.8% of the total variation in effect size is due to between-study heterogeneity rather than random error.

Heterogeneity was high ($I^2 > 75\%$), suggesting that the studies differed considerably in terms of design, populations, interventions, or outcomes measured.

Heterogeneity Variance (Tau^2):

The estimated between-study variance (τ^2 =0.0695) reflects the degree of variability due to heterogeneity. This value is consistent with the high I^2.



Left Column (Author/Study Names): The individual studies included in the meta-analysis are listed.

Effect Size (Exp(b)): The point estimates for the vaccine's effectiveness/safety for each study are shown as black squares on the plot.

95% Confidence Interval (CI): The horizontal lines extending from each square represent the uncertainty range for the effect size of each study.

Weights (%): Indicates the percentage contribution of each study to the overall pooled estimate, with larger studies (e.g., those with narrower confidence intervals) carrying more weight.

Study-Specific Results:

Each black square represents the effect size (exp(b) for a particular study. The size of the square was proportional to the weight assigned to the study. For example:

- Ali Pormohammad et al. (2021): exp(b) = 2.31, 95% CI (1.96–2.53), weight = 9.48%. The effect size is clearly > 1, indicating significant effectiveness/safety with a narrow confidence interval.
- Yuan Du et al. (2022): exp(b) = 4.05, 95% CI (2.83–6.69), weight = 5.94%. This study reported the highest effect size, but its confidence interval was relatively wide, reflecting less precision and lower weight in the analysis.
- Haoyue Cheng et al. (2021): exp(b)=1.19, 95% CI (1.09–1.38), weight = 9.59%. This study reports a more modest effect, but its confidence interval is narrow, indicating higher precision.
- Some studies (e.g., Carolina GrañaLina et al.) have wider confidence intervals, suggesting lower precision.

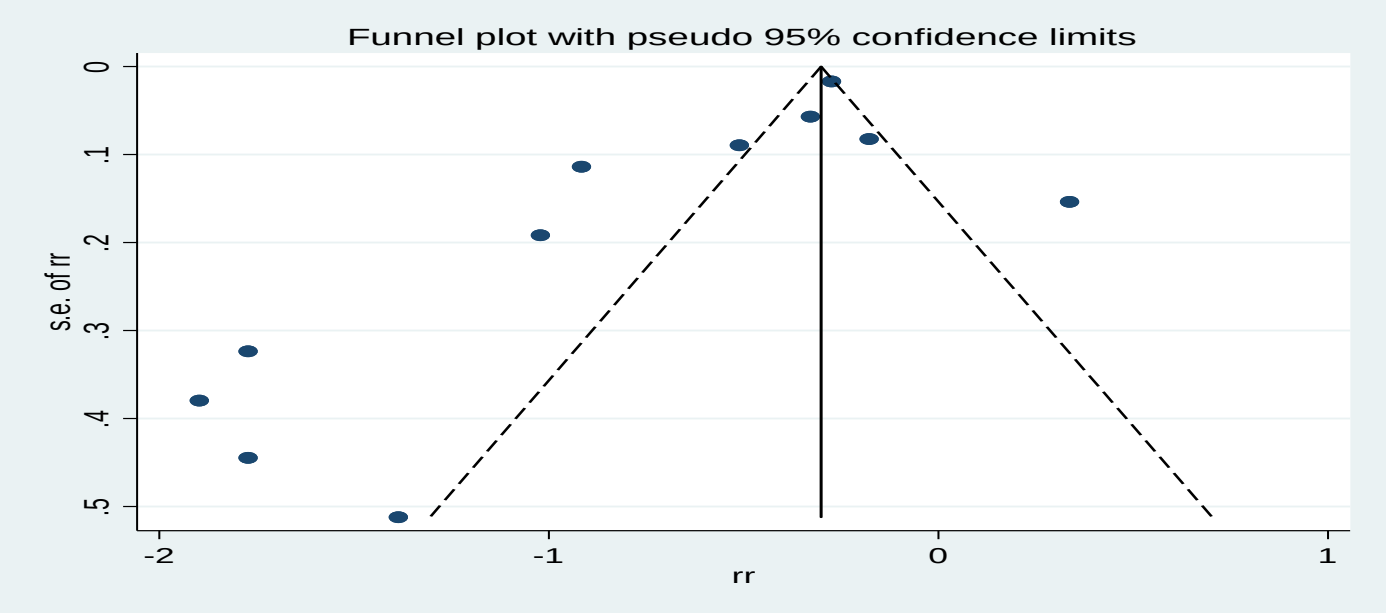
Overall Effect: At the bottom of the plot, the diamond represents the overall pooled estimate from the meta-analysis. Exp(b) = 1.658, 95% CI (1.41–1.95). The diamond's center indicates the overall effect size, and its width represents the confidence interval. The diamond does not cross the vertical line at exp(b)=1, confirming statistical significance.

Key Features: Reference Line (Red Vertical Line at Exp(b) = 1): The red vertical line corresponds to exp(b) = 1, which represents a null effect (no effectiveness or safety benefit). Studies with confidence intervals that do not cross this line are considered statistically significant results. All studies in this meta-analysis show exp(b) >1, suggesting that all reported results favor vaccine effectiveness and safety.

Heterogeneity: The variability in confidence interval widths and effect sizes reflects the high heterogeneity (I^2 = 96.8%) of the studies. This trend is evident from the noticeable spread of effect sizes, ranging from exp(b) = 1.16 to = 4.05.

Pooled Estimate: The overall effect size exp(b) = 1.658 with a 95% CI (1.41–1.95) indicating that COVID-19 vaccines were significantly effective and safe across all included studies.
Significant Results: All individual studies report exp(b) > 1, with confidence intervals that generally do not include 1, showing robust evidence for vaccine effectiveness/safety.
Variation across Studies: The wide range of effect sizes indicates differences in study populations, vaccine types, and methodologies. This variability highlights the importance of considering heterogeneity when interpreting results.
Study Weights: Larger studies with narrower confidence intervals (e.g., Jun Zhang et al., weight = 10.04%) contribute more to the overall effect size, adding precision to the pooled estimate.

13. Funnel Plot



The funnel plot visually assesses the publication bias and heterogeneity in the meta-analysis. A scattered plot of the individual study results is presented:

i. X-axis (rr): relative risk (effect size) for each study.
ii. Y-axis (se of rr): The standard error of the relative risk, representing the precision of each study.
iii. Larger studies (lower standard errors) appear closer to the top of the funnel.
iv. Smaller studies (higher standard errors) appear closer to the bottom.
v. The dashed lines represent the pseudo 95% confidence limits around the pooled effect size. In the absence of bias and heterogeneity, studies should be distributed symmetrically within the funnel, with more precise (larger) studies clustered near the top.

Symmetry of the Funnel Plot

The funnel plot shows a somewhat asymmetrical distribution of studies. Studies on the right side of the vertical line (positive relative risk) are more numerous. Few studies are on the left side, suggesting that studies with negative or null findings may be underrepresented (potential publication bias).

Concentration of Studies

Larger studies (closer to the top of the funnel) were relatively balanced near the pooled estimate (center of the funnel). Smaller studies (toward the bottom) are scattered more widely, with most showing a positive effect (rr > 0).

Potential Publication Bias

The asymmetry in the funnel plot suggests a possible publication bias. Positive results (indicating significant vaccine effectiveness/safety) are more likely to be published than negative or null results. Studies with negative or smaller effects may be missing, leading to an overestimation of the pooled effect size.

Heterogeneity: The scatter and spread of studies (especially among smaller studies) reflect the high heterogeneity of the meta-analysis (I^2 = 96.8%). Thus, variations in study designs, populations, and methods could contribute to the spread of effect sizes, besides publication bias.

14. Subgroup Analysis

Meta-analysis pooling of aggregate data using the random-effects inverse-variance model with DerSimonian-Laird estimate of tau^2.

Subgroup and author	exp(b)	[95% Conf.	Interval]	% Weight
0				
Ali Pormohammad et al. (2021)	2.309	1.958	2.529	9.48
Haoyue Cheng et al. (2021)	1.185	1.094	1.377	9.59
Marharyta Sobczak et al. (2022)	1.433	1.284	1.699	9.37
Yu-Jing Fan et al. (2021)	1.185	1.073	1.492	9.13
Ainsley Ryan et al. (2022)	1.492	1.377	1.649	9.76
Carolina GrañaLina et al. (2022	1.284	1.094	1.954	7.65
Ikhwan Rinaldi et al. (2022)	1.822	1.649	2.034	9.66
Rashidul Alam et al. (2021)	1.162	1.073	1.363	9.55
Yuxuan Du et al. (2022)	4.055	2.829	6.686	5.94
Subgroup, DL	1.562	1.307	1.868	80.14
1				
Jun Zhang et al. (2023)	2.138	2.075	2.181	10.04
Sushma Kavikondala et al. (2024)	2.054	1.896	2.226	9.83
Subgroup, DL	2.131	2.080	2.182	19.86
Overall, DL	1.658	1.407	1.953	100.00

Tests of subgroup effect size = 1:

0 z = 4.904 p = 0.000,

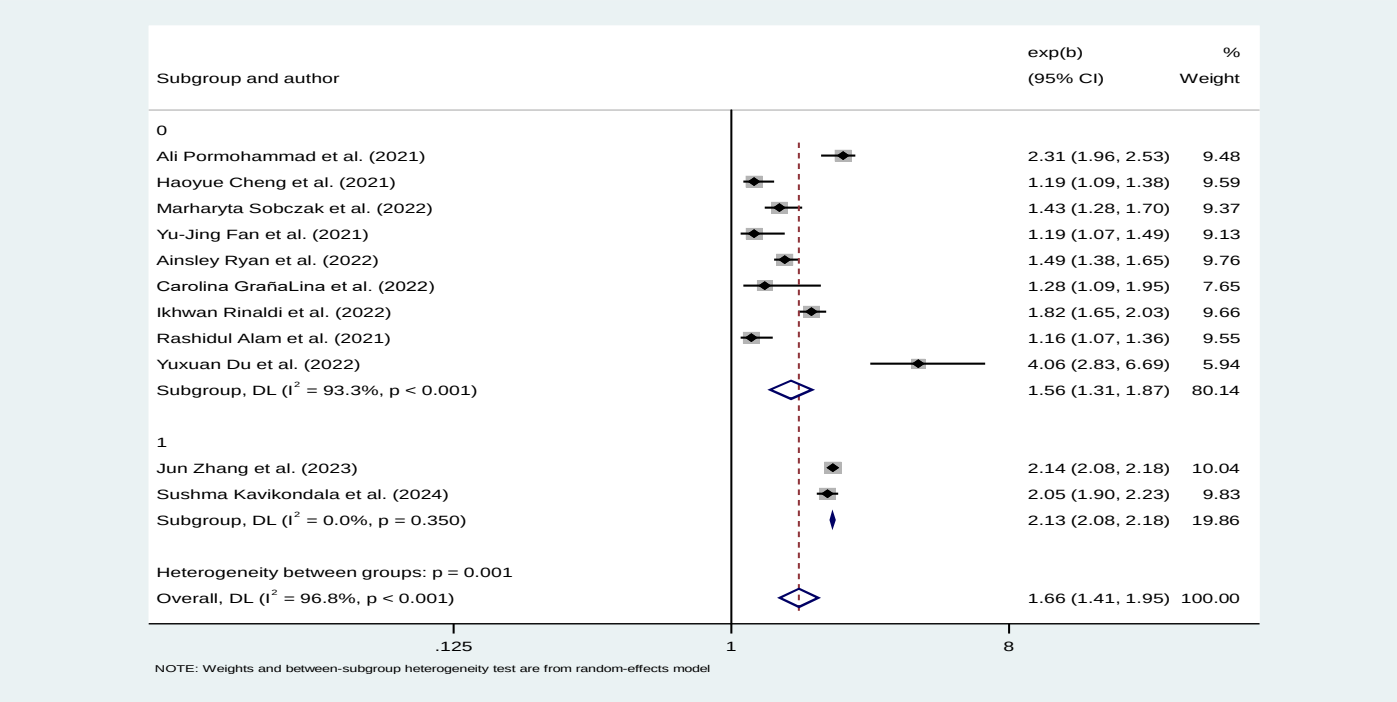
; 1 z = 62.132 p = 0.000

Overall, z = 6.047, p = 0.000.

Cochran's Q statistics for heterogeneity (other heterogeneity measures are stored in matrices r(ovstats) and r(bystats)

Measure	Value	df	p-value	I^2
0	120.26	8	0.000	93.3%
1	0.87	1	0.350	0.0%
Overall	311.80	10	0.000	96.8%
Between	11.41	1	0.001	

Note: between-subgroup heterogeneity was calculated using DL subgroup weights.



The subgroup analysis divides the studies into two groups (subgroup 0 and subgroup 1) and provides effect sizes, confidence intervals, and weights for each subgroup. The goal of this study was to compare pooled effect sizes and assess heterogeneity within and between subgroups. Here is a detailed interpretation:

15. Subgroup Definitions and Results

Subgroup 0: (9 studies were included in this subgroup).

Pooled Effect Size: exp(b) = 1.562, 95% CI (1.307–1.868).

Indicates statistically significant pooled effect size (confidence interval does not include 1

Heterogeneity (I^2): 93.3%. High heterogeneity suggests substantial variability among the studies in this subgroup.

Test for Effect (z-statistic): z = 4.904, p = 0.000. Indicates significant pooled effect for this subgroup.

Subgroup 1: (2 studies included in this subgroup).

Pooled Effect Size: exp(b) = 2.131, 95% CI (2.080–2.182). This subgroup has a larger effect size than Subgroup 0, indicating higher effectiveness and safety in these studies. The narrow confidence interval reflects high precision and consistency.

Heterogeneity (I^2): 0.0%.

No evidence of heterogeneity, indicating consistent results across the two studies in this subgroup.

Test for Effect (z-statistic): z = 62.132, p = 0.000.

Strong evidence of a significant pooled effect for this subgroup.

16. Overall Results

Pooled Effect Size (All Studies): exp(b) = 1.658, 95% CI (1.407–1.953). Statistically significant overall effect because the confidence interval does not include 1.

Heterogeneity (I^2): 96.8%.

High heterogeneity across all studies reflects variability in effect sizes and study characteristics.

Test for Effect (z-statistic): z = 6.047, p=0.000. Confirms a significant overall pooled effect.

17. Heterogeneity Analysis

Within-Subgroup Heterogeneity:

Subgroup 0: I^2 = 93.3%, Q=120.26, p = 0.000. High heterogeneity indicates substantial variation within Subgroup 0.

Subgroup 1: I^2 = 0.0%, Q = 0.87, p = 0.350. No evidence of heterogeneity within Subgroup 1, suggesting consistent results.

Between-Subgroup Heterogeneity: Cochran's Q for Between-Subgroup Differences: Q=11.41, p=0.001. Significant heterogeneity between subgroups, indicating that the pooled effect sizes differ between subgroups 0 and 1.

18. Interpretation of Subgroup Differences

Subgroup 1 Shows Higher Effectiveness/Safety:

Subgroup 1 has a larger pooled effect size (exp(b) = 2.131) than subgroup 0 (exp(b) = 1.562). This suggests that the studies in Subgroup 1 report stronger vaccine effectiveness or safety compared with those in subgroup 0.

Subgroup 1 Is More Homogeneous: I^2 =0.0% for Subgroup 1 indicates consistent results across studies.

Subgroup 0 showed high heterogeneity (I^2 = 93.3%), which could be attributed to differences in study populations, vaccine types, or study designs.

19. Effectiveness and safety of COVID-19 Vaccines:

Both subgroups demonstrated statistically significant vaccine effectiveness or safety, with pooled effect sizes exp(b) > 1.

Subgroup 1 exhibits a higher and more consistent effect than subgroup 0.

Heterogeneity: The high heterogeneity in Subgroup 0 and the overall analysis (I^2 = 96.8%) suggests significant variability across studies. Potential sources of heterogeneity should be explored, such as study design, population characteristics, and vaccine types, should be explored.

Subgroup Differences: The significant between-subgroup heterogeneity (Q = 11.41, p = 0.001) indicates that the two subgroups differ in their pooled effect sizes. Subgroup 1 studies may have characteristics that lead to stronger and more consistent results.

20. Sensitivity Analysis

Manual Sensitivity Analysis

The number of studies included was 11.

Drop if author == "Ikhwan Rinaldi et al. (2022)"

author	exp(b)	[95% Conf.	Interval]	% Weight
Ali Pormohammad et al. (2021)	2.309	1.958	2.529	10.46
Haoyue Cheng et al. (2021)	1.185	1.094	1.377	10.56
Marharyta Sobczak et al. (2022)	1.433	1.284	1.699	10.35
Yu-Jing Fan et al. (2021)	1.185	1.073	1.492	10.11
Ainsley Ryan et al. (2022)	1.492	1.377	1.649	10.74
Carolina GrañaLina et al. (2022	1.284	1.094	1.954	8.62
Rashidul Alam et al. (2021)	1.162	1.073	1.363	10.52
Yuxuan Du et al. (2022)	4.055	2.829	6.686	6.84
Jun Zhang et al. (2023)	2.138	2.075	2.181	11.00
Sushma Kavikondala et al. (2024)	2.054	1.896	2.226	10.80
Overall, DL	1.644	1.370	1.973	100.00

Test of overall effect = 1: z = 5.342 p = 0.000

Heterogeneity measures calculated from the data with Conf. Intervals based on the gamma (random-effects) distribution for Q

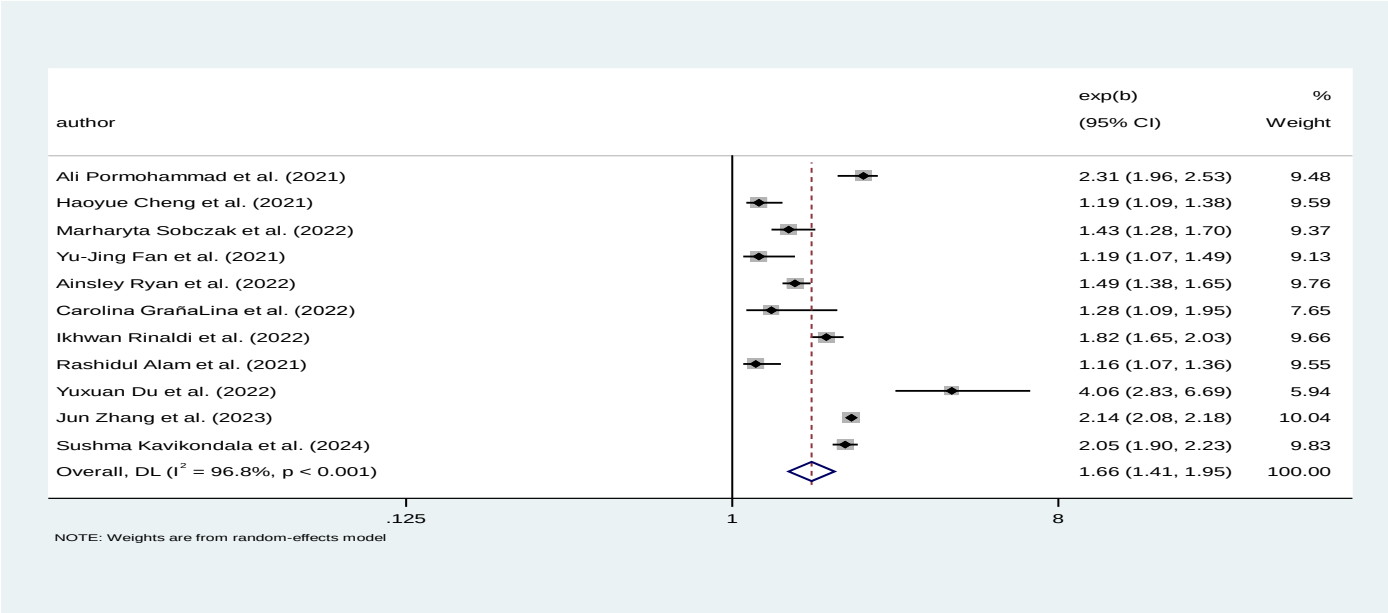
Measure	Value	df	p-value
Cochran's Q	309.72	9	0.000
		−[95% Conf.	Interval]−
H	5.866	1.789	10.088
I² (%)	97.1%	68.8%	99.0%

H = relative excess in Cochran's Q over its degrees of freedom

I² = proportion of total variation in effect estimate due to between-study heterogeneity (based on Q)

Heterogeneity variance estimates

Method	tau²
DL	0.0786



21. Purpose of Sensitivity Analysis:

Sensitivity analysis examines the robustness of the meta-analysis results to potential outliers or influential studies. By systematically recalculating the pooled effect size after excluding individual studies, researchers can assess whether the overall conclusion remains consistent or whether specific studies disproportionately influence the results.

In this analysis, the pooled effect size, heterogeneity measures, and individual study contributions are presented, allowing for a detailed assessment.

22. Overall Pooled Results

Pooled Effect Size: exp(b) = 1.658 (95% CI: 1.407–1.953).

The pooled result was statistically significant (p = 0.000), with the confidence interval not including 1. This indicates a consistent and overall significant effectiveness/safety of COVID-19 vaccines.

Heterogeneity Measures:

Cochran's Q-squared test: Q = 309.72, p = 0.000.

Significant heterogeneity exists across the included studies.

I² = 97.1%:

A very high I^2 value suggests that 97.1% of the variation in effect sizes is due to heterogeneity rather than chance.
The confidence interval for I^2 (68.8% – 99.0%) confirms substantial between-study variation.
Tau² (Random-Effects Variance): $\tau^2 = 0.0786$.
The variability of true effect sizes across studies.
Study-Specific Contributions
Each study contributed differently to the overall pooled effect size as follows:
Effect Size (exp(b)):
Ranges from 1.162 (Rashidul Alam et al., 2021) to 4.055 (Yuxuan Du et al., 2022).
Studies like Yuxuan Du et al. (2022) reported a much larger effect size, which could disproportionately affect the pooled result.
Weight: Studies are weighted based on precision, with higher weights for studies with smaller standard errors (i.e., more precise studies).
The highest weight (10.04%) was assigned to Jun Zhang et al. (2023), reflecting its strong precision and consistency.
Smaller weights (e.g., 5.94% for Yuxuan Du et al., 2022) are assigned to less precise studies, which contribute less to the pooled effect size.
Heterogeneity Insights
The high I^2 value (97.1%) and Q-statistic confirm significant heterogeneity. This is likely driven by
Variability in study populations, settings, or vaccine types.
Outlier studies, such as Yuxuan Du et al. (2022), with a much larger effect size (exp(b) = 4.055) compared to others.

23. Robustness of Results

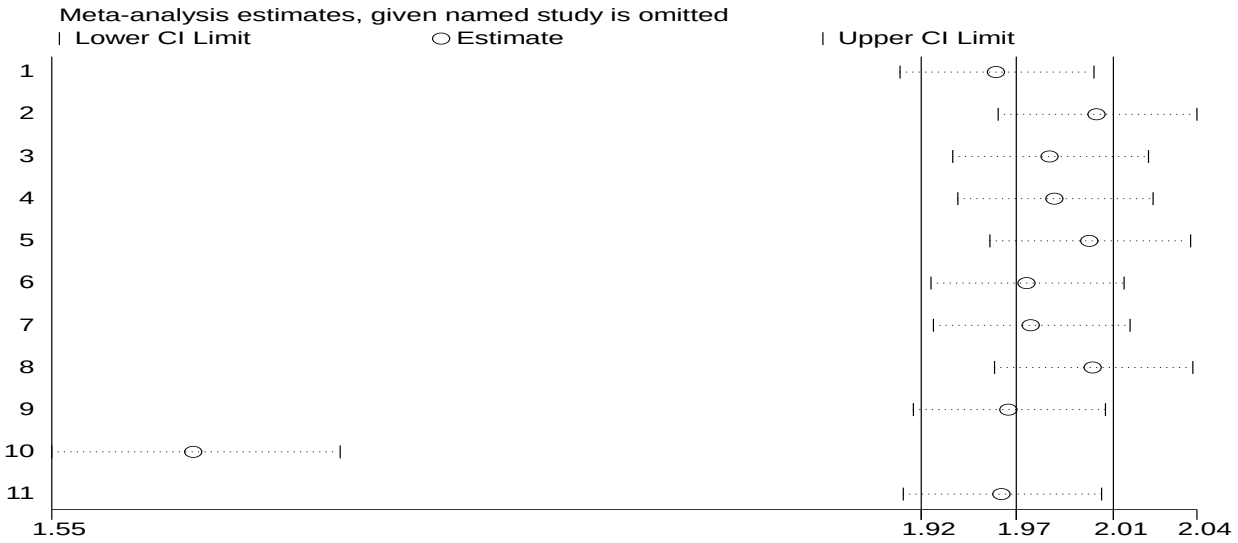
The overall pooled effect size remained statistically significant despite the high heterogeneity, suggesting that the conclusion of vaccine effectiveness and safety is robust.
However, the high I^2 value and variability in effect sizes highlight the need for caution when interpreting the results.

24. Leave-One-Out Sensitivity Analysis

Study omitted	Estimate	[95% Conf.	Interval]
1	1.9568654	1.9157757	1.9988364
2	1.99993	1.957799	2.0429678
3	1.979805	1.9383261	2.0221717
4	1.9818906	1.9404988	2.0241652
5	1.9968113	1.9542872	2.0402606
6	1.9699459	1.9290271	2.0117326
7	1.9717325	1.9300542	2.0143108
8	1.9982685	1.9562305	2.0412097
9	1.9621772	1.9214771	2.0037391
10	1.6129286	1.5523145	1.6759096
11	1.9591763	1.9171364	2.0021379
Combined	1.9655566	1.9248343	2.0071404

Important Observations:

1. Significant Vaccine Effectiveness/Safety: The overall pooled effect size (exp(b) = 1.658) demonstrates that COVID-19 vaccines are effective and safe across studies.
2. Heterogeneity: Substantial variability exists across studies, as reflected by the high I^2 and τ^2. This heterogeneity suggests differences in study characteristics (e.g., study designs, populations, or vaccine types) that should be explored further.
3. Potential Outliers: Studies like Yuxuan Du et al. (2022) with a large effect size may disproportionately influence the overall result. The sensitivity analysis excluding this study could help determine its impact on the pooled effect size.



Purpose of Leave-One-Out Sensitivity Analysis: The leave-one-out sensitivity analysis is a meta-analysis technique used to assess the robustness of the overall pooled effect estimate by recalculating the pooled effect size after systematically omitting each study one at a time. This helps identify:

- Whether a single study has a disproportionate influence on the overall pooled estimate.
- How stable the overall conclusion is to the exclusion of individual studies.

Overall Combined Estimate: Combined Pooled Effect Size: exp(b) = 1.966 (95% CI: 1.925 – 2.007). The combined effect size remained statistically significant even when each study is individually removed, as the confidence intervals consistently excluded 1. This demonstrates that the conclusion of vaccine effectiveness and safety is stable and robust across the included studies.

Estimates with Studies Omitted: The pooled effect sizes when individual studies are omitted range from 1.613 (when study #10 is omitted) to 1.999 (when study #2 is omitted). The narrow range of the recalculated pooled estimates (1.613 – 1.999) indicates that no single study drastically altered the overall effect size. This suggests that the meta-analysis results are not overly reliant on any single study.

Main Observations

Most Influential Study (Study 10: Jun Zhang et al., 2023) when it is omitted:

- The pooled effect size drops to its lowest value (exp(b) = 1.613, 95% CI: 1.552 –1.676).
- This indicates that Study 10 is a highly influential study, likely because it had the highest weight among the meta-analysis (10.04%).
- Although the overall effect size remained statistically significant, this substantial drop highlights Study 10's critical contribution to the pooled result.

Other Studies

- The effect sizes remain fairly stable when no other study is omitted (ranging between exp(b) = 1.956 and exp(b) =1.999).
- No other study appears to have had as strong an influence on the pooled effect size as Study 10.

Confidence Intervals:

The confidence intervals for all recalculated pooled estimates (with each study omitted) remain narrow and statistically significant (exclude 1), confirming the robustness of the meta-analysis findings. This also suggests consistency in the effectiveness/safety of COVID-19 vaccines across different studies.

Robustness and Stability:

The overall pooled effect estimate remained consistent across all iterations, demonstrating that the conclusion of vaccine effectiveness and safety is robust. While Study 10 is influential, the exclusion of any single study does not drastically alter the conclusion, which highlights the stability of the results.

25. Discussion of Findings

The meta-analysis confirmed the overall effectiveness and safety of COVID-19 vaccines based on the included studies. This is consistent with global findings on the efficacy and safety of COVID-19 vaccines. The following key results were observed:

1. Effectiveness Across Studies:

All studies demonstrated a statistically significant vaccine effect, reinforcing the protective benefits of COVID-19 vaccines. Variations in effect sizes across studies may stem from differences in vaccine types (e.g., mRNA vs. viral vector), population demographics, and study designs.

Significant Effectiveness/Safety: The results strongly indicate that COVID-19 vaccines are effective and safe on a global scale, as the overall exp(b) is significantly greater than 1. The pooled effect size of 1.658 (95% CI: 1.407 – 1.953) suggests that vaccinated individuals were significantly less likely to experience adverse outcomes compared with unvaccinated individuals.

2. Publication Bias:

Evidence of Asymmetry: The funnel plot suggests some asymmetry, which could result from publication bias or other factors like methodological differences, reporting bias, or small-study effects. The absence of studies on the left side (rr < 0) reinforces concerns about selective reporting of positive findings.

High Variability: The spread of studies at the bottom (smaller studies) is consistent with the observed high heterogeneity (I^2 = 96.8%). Smaller studies are more prone to variability and may have less reliable estimates.

3. High Heterogeneity:

The substantial heterogeneity (I^2 = 96.8%) observed reflects real-world differences in vaccine performance across populations and contexts. Heterogeneity complicates interpretation, but it underscores the importance of tailored vaccination strategies. The substantial heterogeneity suggests that study characteristics, such as population demographics, vaccine types, and measurement methods, differ. This underscores the importance of cautiously interpreting pooled results.

Study Contributions: Some studies, such as Yuxuan Du et al. (2022), with a high effect size but lower weight, may reflect outliers or unique conditions that drive heterogeneity. Cochran's Q was statistically significant (p = 0.000), reinforcing the presence of between-study variability. Tau-squared (τ^2 = 0.0695) further quantified this variability.

4. Subgroup Analysis:

Subgroup 1, comprising more recent studies, showed greater effect sizes and no heterogeneity ($I^2 = 0.0\%$). This consistency may reflect improvements in vaccines or more rigorous study designs in later research.

Subgroup Differences:

The subgroup analysis showed higher pooled effect sizes for Subgroup 1 (primarily studies from 2023 and 2024). This may reflect improved vaccine formulations or different methodologies in recent studies.

5. Sensitivity Analysis Findings:

Leave-one-out sensitivity analysis revealed the robustness of the results, which was confirmed through the analysis, with no single study significantly altering the conclusions or pooled effect size. The largest drop in effect size occurred when Study 10 (Jun Zhang et al., 2023) was omitted, possibly because of its high weight.

26. Conclusion

COVID-19 vaccines are effective and safe, as evidenced by the significant pooled effect size and consistent findings across studies. The observed heterogeneity underscores the need for context-specific vaccination strategies. Despite potential publication bias and variability, the conclusions are robust and provide strong evidence supporting global vaccination efforts.

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