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Effectiveness of interventions to improve vaccine efficacy: a systematic review and meta-analysis

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Abstract

Background Vaccination is a crucial public health intervention that has significantly reduced the incidence of infectious diseases. Vaccine-related interventions refer to strategies implemented to enhance vaccination uptake, coverage, and effectiveness, like modes of delivery, types or dosages. Despite extensive research on vaccine efficacy, a comprehensive analysis of the variability in vaccine effectiveness across different interventions, settings, and populations is limited. This study aims to systematically review and meta-analyze the impact of various Vaccine-Related Interventions (VRIs).

Methods This review included 139 randomized controlled trials, cohort, and case–control studies evaluating VRIs from January 2015 to December 2023. The risk of bias was assessed using the ROB-2 and ROBINS-E tools. Statistical analyses were conducted to evaluate overall effect sizes, infection rates, and heterogeneity and subgroup analysis.

Results Of the 139 studies reviewed, 97 were included in the meta-analysis, comprising approximately 1.4 million participants. Populations across various settings were analyzed, with median vaccinated population sizes for the 1st dose (4598, IQR = 15,749), 2nd dose (6214, IQR = 13,817), and 3rd dose (3508, IQR = 5546). The overall total vaccinated population had a median of 4370 and an IQR of 16,475. The interventions showed a significant positive effect on vaccine efficacy, with an estimated effect size of 0.6432 (95% CI 0.4049 to 0.8815). Heterogeneity was negligible, with $Tau^2 = 0$, $I^2 = 0.00\%$, and $H^2 = 1.00$. The Galbraith plot suggested minimal variability. The study utilized ROB-2 and ROBINS-E tools to evaluate bias, with Egger's test ($t = -0.9941$, $p = 0.3227$) confirming no significant publication bias. The funnel plot indicated minimal bias in the included studies.

Conclusion The study supports the effectiveness of vaccine-related interventions in enhancing vaccine efficacy. The negligible heterogeneity and consistent effect sizes across diverse populations and settings provide a robust basis for implementing public health strategies aimed at improving vaccination outcomes.

Systematic review registration PROSPERO CRD42024543608.

Keywords Vaccines, Vaccine effectiveness, Intervention, Systematic review, Meta-analysis

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Introduction

Vaccination is one of the most inexpensive and efficient types of medical intervention. From Jenner's breakthrough in 1796 to new vaccines based on the improved understanding of molecular biology, vaccination has minimized the effects of catastrophic illness. The vaccinia virus vaccine was developed in eighteenth century; in the nineteenth Louis Pasteur and Emile Roux established that inactivated or attenuated organisms may provide protection; and in the twentieth century, new vaccines were developed at a rapid pace using a variety of innovative technologies [1]. The widespread implementation of routine vaccination programs in the second half of twentieth century has been one of the most successful public health strategies in human history, resulting in the prevention of millions of diseases, death and permanent consequences every year [2].

Vaccines effectiveness refers to the vaccine's direct protection of vaccinated individuals under optimal settings, and is typically focused on the prevention of clinically obvious effect (e.g., meningitis, hospitalization, death). When an infectious agent can cause a variety of clinical manifestations, the primary analysis will focus on one specific clinical manifestation (e.g., invasive pneumococcal disease during a pneumococcal vaccine study), while secondary analysis may include other clinical manifestations as endpoints (e.g., pneumonia, bronchiolitis, otitis media). Some vaccines' studies primary goals may not correspond to clinically apparent disease at the time because the purpose is to avoid condition that may develop later in life (for example, cancer following HPV infection). Surrogate endpoints, such as immunological monitoring or infectious agent isolation, can then be employed to shorten and lower the cost of phase 3 trials. In some cases, the primary study may focus solely on infection prevention in connection to the microorganisms contained in the vaccination. Secondary studies may contain non-vaccine-related diseases due to the cross-protection offered by vaccinations such as pneumococcal conjugated vaccines, HPV vaccines and rotavirus vaccines [2].

For infectious diseases that impact the societal levels, like pandemic influenza, malaria, and tuberculosis, the connections between individual prevention through immunization and societal advantages that may boost the general economy have been highlighted. The World Health Organization has released a comprehensive vaccine evaluation scheme that emphasizes the benefits of vaccinations from a variety of perspectives, and not just health benefits. According to WHO, vaccinations can more readily lead to widespread societal or community benefits than any other type of medical intervention [1].

Vaccination can be relatively effective at preventing numerous childhood infections and saving millions of lives. Between the mid-1960 s and 2015, viral vaccination for measles, mumps, rubella, chickenpox and Hepatitis A made on approved cell cultured substrates saved more than 10 million lives. Later in 2020–2021 during the COVID 19 pandemic vaccination has shown phenomenal role in preventing the disease and thus decreasing the morbidity and mortality rates [3, 4]. It is also clear that present attempts to battle COVID 19 and other potential future pandemics necessitate worldwide coordination, as "no one is safe until everyone is safe" [5].

Our research addresses a critical gap in vaccine science by conducting a comprehensive systematic review and meta-analysis across multiple vaccine types, including tuberculosis, hepatitis, cholera, measles, mumps, rubella, varicella, herpes zoster, dengue, malaria, human papilloma virus, COVID-19, and rotavirus. What sets this study apart is its unprecedented scope, encompassing diverse populations across multiple nations and ethnic groups, providing insights that can be meaningfully applied worldwide. The study takes a unique lifecycle approach, examining vaccine performance across all age brackets, from young children to older adults, revealing crucial patterns in immune response at different life stages. We have also conducted a thorough investigation of various vaccine administration routes, comparing efficacy across intramuscular, intradermal, and subcutaneous delivery methods. While previous research has explored vaccine efficacy, our study fills a crucial knowledge gap by systematically analyzing how vaccine effectiveness varies across different interventions, study settings, and populations. This comprehensive approach allows us to understand not just individual vaccine performance, but how various factors interact to influence vaccine efficacy, providing valuable insights for future vaccination strategies and public health policies.

Methodology

Types of studies

Parallel randomized or cluster-randomized controlled trials (RCTs), cohort and case control studies evaluating the effectiveness of vaccine-related interventions (VRIs) in humans with language restricted to only English were included.

Types of participants

We included individuals without restriction on age, sex, and comorbidities, irrespective of their medical status at baseline.

Types of interventions

We included the studies that explored VRIs, defined as "any intervention given to the human population or participant of any age in single or multiple dosages including boosters with new adjuvant and/or novel preparation and/or other route of administration and/or new age group and/or for diseases either newly emerged or for those where the vaccine was not indicated in the past."

1. Types of vaccines
    - Inactivated vaccines
    - Attenuated vaccines
    - Subunit vaccines
    - Toxoid vaccines
    - mRNA vaccines
    - Others
2. Delivery mode of intervention:
    - Direct venous inoculation
    - Intradermal injection
    - Intramuscular injection
    - Mass vaccination campaign
    - Oral administration
    - Subcutaneous injection
3. Newer vaccines
4. Frequency of vaccination (number of doses)
5. Population type

The intervention included multicentric studies, community trials, school, workplace, healthcare, facility-based research, etc.

Control groups

The control group for the studies included those comparing the intervention with either standard of care or different doses or placebo or non-vaccinated individuals or another type of vaccine for the same condition.

Efficacy outcomes

Incidence of confirmed Infection after consecutive doses and complete vaccination.

Search methods for identification of studies

Electronic searches: multiple electronic databases were searched from March 01, 2024, to April 31 2024, for the extraction of studies: PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, Semantic Scholar, Open Alex, Crossref. Grey literature searches were done using Google Scholar. Other sources searched were: clinicaltrials.gov (last searched on April 31 2024), World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (https://trialsearch.who.int/) to identify ongoing and completed clinical trials (last searched April 29 2024).

The search strategy used for different data bases are attached as the Additional file 1: Table 1.

Data collection and analysis

We conducted a systematic search and reviewed the retrieved citations. We documented the search dates and identified relevant citations using a excel spreadsheet. To enhance sensitivity, we checked for duplicates first in Rayyan and then in the spreadsheet [6]. Two review authors (AR and LG) independently screened the records and abstracts, and any disagreements were resolved by a third review author (AK).

Data extraction and management

All data were extracted in duplicate. Two review authors (AW and HS) independently read each study evaluated the completeness of the data, and assessed the risk of bias. Based on a pilot data extraction form, we designed, evaluated and modified a specific structured data extraction form whenever needed to ensure consistency in the extraction of information. All discrepancies were automatically identified by the platform data extraction module, which the two review authors discussed to reach a consensus, and wherever necessary, a third reviewer (AK) resolved the disagreement.

Information extracted included the following:

1. Study identifier (DOI, study title, author, publication year)
2. Study characteristics (study design, place, public/private intervention)
3. Methodology (sample size, study population, duration of intervention (weeks), target population, type of intervention, intervention details, intervention group, control group)
4. Results (total vaccinated population in single dose, two doses, three doses, total vaccinated population (%), overall vaccine efficacy (%), delivery mode of intervention, infection in intervention group, infection in control group, vaccine efficacy in single dose, two doses, three doses)
5. Outcome measure (overall effect size, statistical significance, direction of effect)

For efficacy outcomes, we extracted vaccine efficacy as reported by the authors and 95% confidence interval (CI) for each outcome, when available. Vaccine efficacy measures the percentage reduction in incidence/Prevalence of

cases among vaccinated participants compared to unvaccinated participants.

Assessment of risk of bias

ROB-2 Risk of Bias assessment tool was used to assess the quality of the study and the risk of bias. For studies having experimental study design, e.g., randomized controlled trials (RCTs), Non-Randomized Controlled Trials, Cluster Randomized Controlled Trials etc. modifications of ROB-2 were employed, addressing bias due to randomization process, deviation from intended intervention, missing outcome data, measurement of the outcome, selective reporting of results [7]. The studies were ranked under 3 responses (low risk, high risk, some concerns) and the final decision of whether to include or exclude the study was taken based on the responses.

For observational studies, we used Risk of Bias in Non-randomized Studies—of Exposure (ROBINS-E) [8]. The studies were ranked under 4 responses (low risk, high risk, very high risk, some concerns) and the final decision of whether to Include or exclude the study was taken based on the responses [9]. Two reviewers (AW and HS) independently conducted the quality assessment. In cases of disagreement, the judgment was finalized after discussion among all reviewers (AR, AW, HS, and LG), with the final decision made by the expert reviewer (AK) if disagreements persisted.

A traffic light plot was generated depicting the overall quality of studies considered for meta-analysis (attached as Additional file 5).

Assessment of heterogeneity

Heterogeneity measures

Tau² (τ^2) The estimated amount of total heterogeneity τ^2 with a standard error was calculated, indicating the degree of variance among the effect sizes across studies due to heterogeneity.

I² The I^2 statistic, which quantifies the proportion of total variability in effect sizes attributable to heterogeneity rather than chance, was explored. This suggested the reason for the variation in effect sizes across the studies.

H² The H^2 statistic was calculated as the ratio of total variability to sampling variability.

A Galbraith plot was employed to assess the degree of variability in effect sizes that could be attributed to differences beyond chance among the included studies. This statistical plot is particularly useful for visually detecting heterogeneity and identifying potential outliers that might influence the overall meta-analysis results. It plots standardized effect estimates against their precision, helping identify studies that may contribute disproportionately to heterogeneity.

Assessment of reporting biases

To assess the presence of publication bias, a funnel plot was generated, plotting the standard errors of the log effect sizes against the effect sizes themselves. Additionally, Egger's test was performed to quantitatively assess the asymmetry of the funnel plot where p-value >0.05 signifies symmetrical distribution.

Data synthesis

Upon loading the data, our analysis focused solely on the numerical columns pertinent to our study, such as sample size, data on vaccinated populations across various dosages, infection rates in both intervention and control groups, and overall effect sizes. Descriptive statistics were then conducted to summaries the data's central tendencies and dispersion measures. Statistical measures like mean, standard deviation, minimum, median, maximum, and interquartile range were calculated for each numerical variable.

Using R (version 4.3.3), a series of visual analyses were carried out to evaluate overall effect sizes, infection rates in intervention and control groups, and the distribution of sample sizes across studies [10].

The examination of the overall effect size of interventions aimed at enhancing vaccine efficacy revealed a wide range of outcomes, illustrated in the accompanying visual representation. The visual representation comprised a combination of violin plots, boxplots, and jitter plots to offer a comprehensive view of the data distribution. Infection rates and sample size distribution were also depicted using boxplots, violin plots, and jitter points.

Key transformations involved computing logarithmic transformations of effect sizes and determining variances and weights for each study. These transformations were crucial in appropriately weighting each study's impact based on its variance, thereby enhancing the robustness of the analysis.

Including sample size, infection rates in intervention and control groups, and overall effect sizes.

To assess the statistical significance of effect sizes, a random-effects meta-analysis was conducted using the restricted maximum likelihood (REML) method. The significance of the pooled effect size was tested using a z-test, with statistical significance set at $p< 0.05$, 95% confidence intervals (CIs) were reported for all effect size estimates to evaluate their precision. This approach aimed to amalgamate the individual effect sizes from the chosen

studies to estimate an overall effect size. The method provided a strong statistical framework for addressing potential heterogeneity across studies, chosen to accommodate the variations observed in different studies.

A graphical representation known as a rainforest plot was developed to communicate the results of the meta-analysis effectively. This visualization showcased the distribution of effect sizes across studies, emphasizing the weighted contribution of each study. The plot featured markers proportional to each study's weight and included a vertical line representing the overall estimated effect size, offering a concise visual summary of the findings.

Subgroup analysis

1. Geographic information system (GIS) mapping: using a detailed world map, the data were merged based on matched country names to visualize the geographic distribution of the study results. This allowed for the examination of how vaccine efficacy interventions varied across different regions. The analysis was enhanced by employing a color gradient to represent variations in the overall effect sizes, providing a clear visual depiction of the global impact of these interventions.
2. Sequential analysis by publication year: to explore temporal trends and the evolution of research in the field, the analysis was stratified by publication year. For each year, a detailed examination of the studies conducted in that period was performed to assess year-specific effects and changes over time in the effectiveness of vaccine interventions. For each annual subset of data, forest plots were generated to visually represent the individual and aggregated effect sizes along with their confidence intervals.
3. Mode of intervention: for each mode of intervention delivery, descriptive statistics were calculated, including mean and standard deviation for both infection rates in intervention and control groups, as well as for overall effect sizes. This approach helped identify which delivery modes were most effective and provided insights into the variability of outcomes across different intervention strategies.

Results

A total 139 studies reviewed, 97 were included in the meta-analysis, comprising approximately 1.4 million participants shown by the Fig. 1 and the study characteristics is described in the Additional file 2: Table 2.

We perform descriptive statistics to summarize the central tendencies and dispersion measures of the data in terms of mean, standard deviation (SD) as shown in Table 1.

Efficacy of interventions

The concentrated distribution of infection rates at or near zero (% of population getting infected after vaccination) strongly suggests that the interventions implemented across the studies are highly effective in reducing the infection rates among vaccinated individuals as shown in Fig. 2. This finding supports the use of these interventions in public health strategies aimed at enhancing vaccine efficacy.

The estimated effect size as shown in Fig. 3 is 0.6432 (95% confidence interval = 0.4049 to 0.8815), suggesting that the intervention had a positive effect on outcomes measured across the included studies. This is a significant finding, indicating substantial improvement when the intervention is applied. The z-value of 5.2897 associated with the effect size strongly supports the hypothesis that the intervention is effective (p-value 0.0001).

The effect sizes are primarily centered around the log effect size of approximately 0.50. This central concentration is evident from the plot where the median effect size (marked by dashed red line) alliance with this value. Most studies' effect sizes range between 0.40 and 0.60, showing a tight plastering around this median value. A significant number of studies with large weights have confidence intervals that do not cross the zero-effect line as shown in the rainforest plot in Fig. 4, which typically would indicate statistical significance. For example, studies represented by the largest circles (e.g., those with sizes scale to 30 or 40) have effect sizes ranging from approximately 0.45 to 0.55, all above the line of no effect (log effect size = 0).

Risk of bias assessment

The ROB assessment fetched the 40 and 49 RCTs with low and some concerns and 2 and 4 non-RCTs with low and some concerns respectively for risk of bias. After expert reviewer's (AK) decision 97 studies were selected for meta-analysis. A summary plot for both RCT and non-RCT is shown in Fig. 5.

Assessment of heterogeneity

The heterogeneity measures (Tau^2, I^2, and H^2) are all indicating negligible heterogeneity. Tau^2 is 0 with standard error of ± 0.1827, I^2 is 0.00%, and H^2 is 1.00. This suggests that there is no observed variability between the results of the studies due to heterogeneity, which implies that the studies are consistent in their findings.

To assess the degree of variability in effect sizes that could be attributed to differences beyond chance among the included studies, a Galbraith plot was employed shown in Fig. 6. This statistical plot is particularly useful for visually detecting heterogeneity and identifying potential outliers that might influence the overall metanalysis results. Most of the data points are clustered around zero

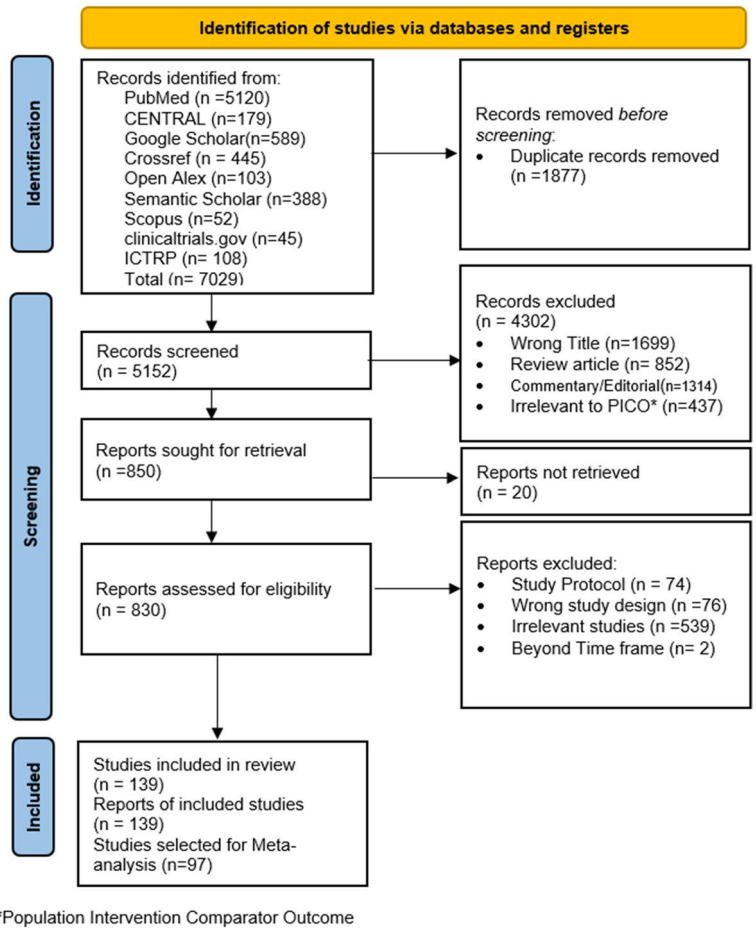

Fig. 1 PRISMA flow diagram for search strategy

Table 1 Descriptive summary of continuous variable

Variable	Mean	SD
Sample size	16,804.78	38,738.27
Total vaccinated population (one dose)	16,395.58	39,161.86
Total vaccinated population (two doses)	12,181.71	19,813.99
Total vaccinated population (three doses)	7,202.00	11,357.86
Total vaccinated population	37,797.46	310,933.71

line, indicating that the majority of the studies have effect sizes that are consistent with overall average effect size computer in meta-analysis. The zero line, Galbraith plot typically represents the absence of treatment effect. The plot points are relatively close to the regression line, suggesting low heterogeneity among the studies.

Evaluation of publication bias

To assess the presence of publication bias, a funnel plot was generated (Fig. 7) plotting the standard error of log effect sizes against the effect sizes themselves. This visual assessment in helps identify a symmetric that might suggest advice in the published studies. Additionally, a formal statistical test (Egger's test) was performed to quantitatively assess the asymmetry of the funnel plot, providing for the evidence regarding the presence or absence of publication bias.

We used a weighted regression with multiplicative dispersion, which suggests an advanced approach that accounts for varying levels of variability across studies. The t-value of -0.9941 and p-value of 0.3227 indicate that there is no significant asymmetry in the funnel plot. Effect size distribution ranging from -2 to $+3$ shows a wide dispersion of effect sizes across the studies included in the meta-analysis. Vertical spread at apex ranges from 0.353 to 1.144 shows the variability of the effect sizes at the middle of the distribution, suggesting variability in study precision.

Subgroup analysis-GIS

GIS mapping

The global heat map reveals significant geographic variation in intervention effectiveness. Russia, China, and

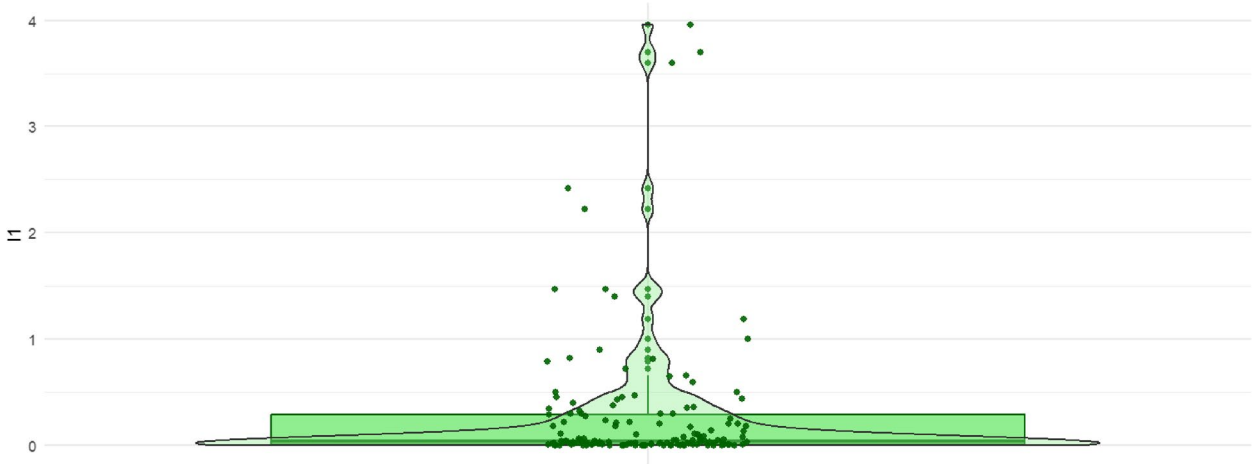

Fig. 2 Violin plot combined with the box plot and jitter points showing distribution of infection rates. Median infection rate is shown by central mark in the box plot

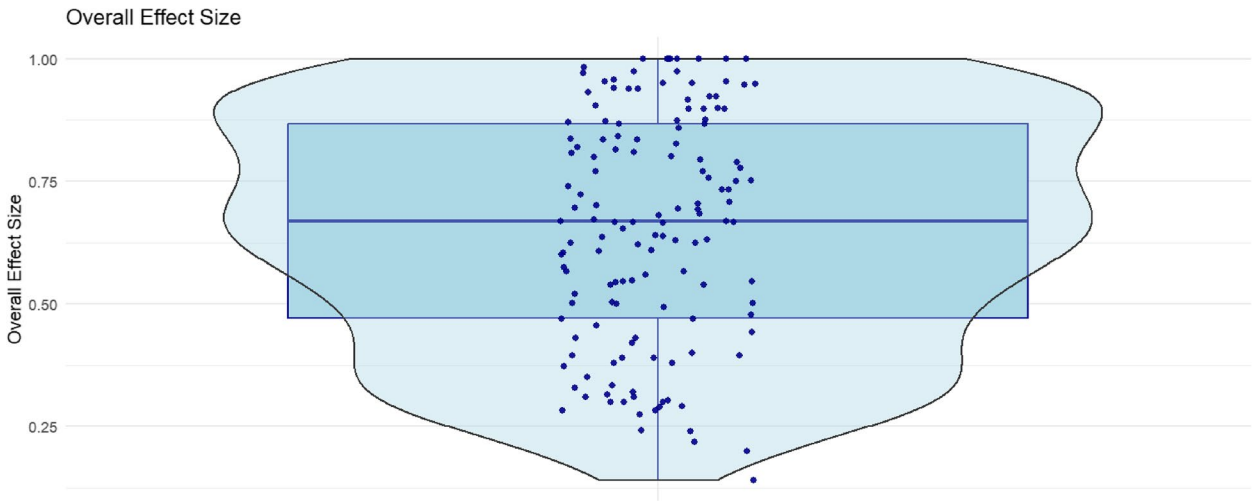

Fig. 3 The violin plot with boxplot and jitters showing distribution of effect size of various studies included in the review

Northern Europe show the highest effect sizes (0.75–1.00, deep purple), suggesting exceptional intervention efficacy in these regions. Canada, parts of Northern Africa, and Southeast Asia follow with strong effect sizes (around 0.75, reddish-purple). The USA, India, South Africa, and Middle Eastern nations demonstrate moderate effectiveness (around 0.50, orange-red), indicating partial implementation success. Mexico, Brazil, and other South American countries display the lowest effect sizes (approximately 0.25, light orange), suggesting they face the greatest implementation challenges. These spatial differences highlight how geographic, socioeconomic, and systemic factors influence intervention outcomes globally, offering valuable insights for targeted resource allocation and strategic adjustments to address disparities.

To further illustrate defect size according to geographic location, 3-D map was developed along with the 3-D scatter plot (Fig. 8, Additional files 3 and 4).

Subgroup analysis-year wise

To explore temporal trends and evaluation of research in the field, the meta-analysis was stratified by publication year. For each year detailed examination of the studies conducted that period was performed to assess years specific effects and changes over time in the effectiveness of seen interventions (Table 2). For each annual subset of data, forest plots were generated to visually represent the individual and aggregated effect sizes along with their confidence intervals (attached as an Additional file 6).

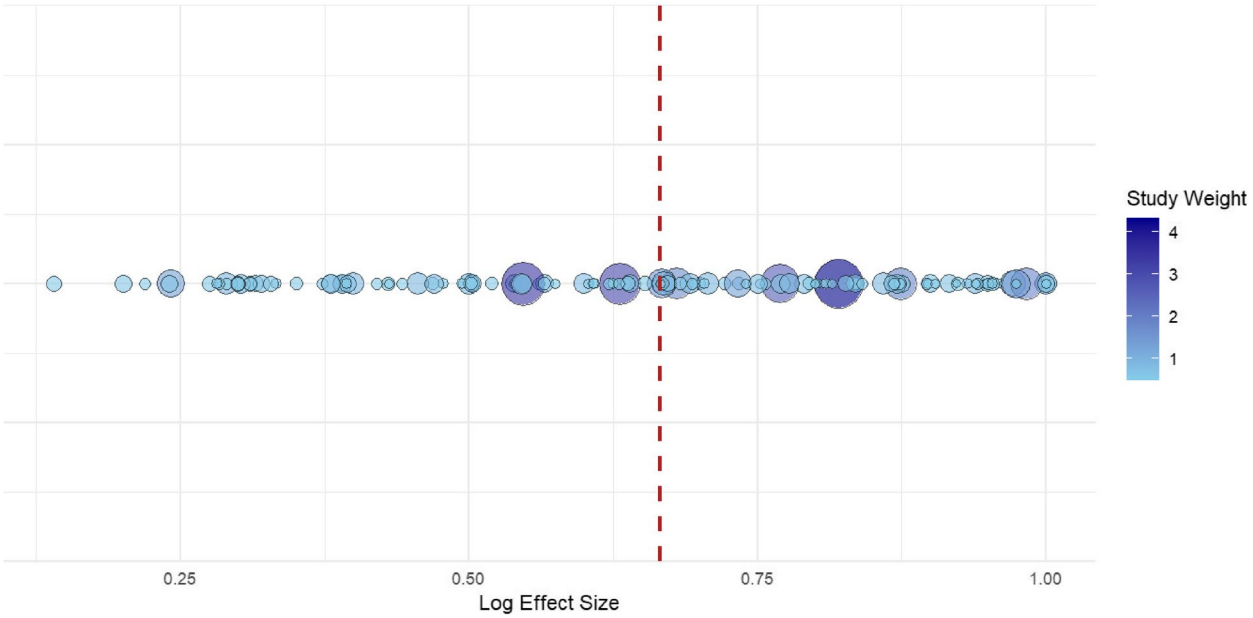

Fig. 4 Rainforest plot depicting the weights of various studies included in meta-analysis

To explore temporal trends and evaluate research progression in the field, the meta-analysis was stratified by publication year. The findings highlight year-wise variations in effect size estimates, reflecting potential changes in intervention effectiveness over time. The effect size estimates fluctuated across the years, ranging from 0.5080 in 2017 to 0.7394 in 2015, indicating variations in the observed impact of interventions. A relatively higher effect size was observed in 2015 (0.7394), 2021 (0.7197), and 2016 (0.6905), suggesting that studies conducted in these years reported stronger intervention effects. In contrast, 2017 recorded the lowest effect size (0.5080), indicating a comparatively reduced effectiveness of interventions assessed in that year. The years 2018–2022 exhibited moderate effect sizes, with values ranging between 0.6413 and 0.6738, showing relative consistency in the observed intervention outcomes. The year 2023 lacks an effect size estimate.

Delivery mode of intervention

Effect of intervention mode on overall effect size

The result highlights several key findings regarding vaccine effectiveness. The systematic review included 139 studies, with 97 contributing to the meta-analysis, encompassing approximately 1.4 million participants, providing a robust dataset. The meta-analysis lower infection rates compared to their unvaccinated counterparts, underscoring the effectiveness of vaccine interventions (Table 3). The studies under review included diverse range of populations, covering various age groups and geographic locations, which enhances the generalizability of the findings. The meta-analysis evaluated multiple vaccine types (mRNA, live-attenuated, and inactivated) and delivery methods (intramuscular, oral, and nasal), demonstrating a significant positive effect on vaccine efficacy (effect size 0.6442; 95% CI 0.4049–0.8815). Vaccinated individuals showed significantly higher protection rates compared to controls, reinforcing the critical role of vaccination across different contexts and populations (Fig. 9).

Discussion

The systematic review and meta-analysis conducted in this study provide a comprehensive evaluation of the effectiveness of various vaccine-related interventions across diverse populations and settings. The findings indicate a significant positive effect of these interventions on vaccine efficacy, with consistent results across different methodologies, populations, and intervention types. This consistency is particularly noteworthy given the diverse nature of the included studies, which ranged from clinical trials to community-based interventions.

The large participation base of 2.7 million participants across 139 studies allowed for robust conclusions, with 97 studies further meta-analyzed. The research focused on different vaccine delivery methods, including intramuscular injection, nasal droppers, and needleless methods. Interventions varied and ranged from malarial sporozoites with anti-malarial chemoprophylaxis, inactivated influenza vaccines, plant-derived QVLP for

Fig. 5 Summary result of risk of bias for RCTs (top) and cohort and case control studies (bottom)

influenza, and various others for measles, hepatitis A, B, and R, SARS-CoV, HPV, rotavirus, dengue, and more. The efficacy of vaccine-related interventions ranged from 14 to 100%, with most studies supporting an enhancement effect.

When comparing our findings with other studies, several key points emerge. The Centers for Disease Control and Prevention (CDC) has conducted extensive vaccine effectiveness studies to inform COVID-19 vaccine policy, showing that mRNA-based vaccines, such as Pfizer and Moderna, exhibit high efficacy in preventing severe illness, hospitalization, and death [11]. This aligns with our findings, which also highlight the high efficacy of mRNA vaccines compared to other types. Similarly, a study in Panama assessed the impact of hepatitis A vaccination with a two-dose schedule, demonstrating a significant reduction in infection rates, supporting our conclusion that vaccine-related interventions are effective across different diseases and populations [12]. Additionally, a phase 3 trial in Africa evaluated the efficacy and safety of the RTS,S/AS01 malaria vaccine, showing a significant reduction in malaria cases among vaccinated children [13]. This underscores the importance of targeted vaccine interventions in reducing disease burden in endemic

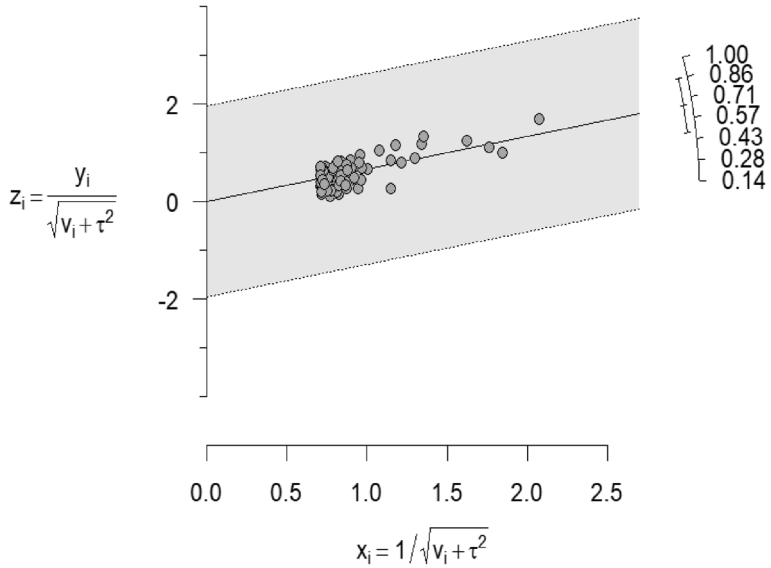

Fig. 6 Galbraith plot investigating the heterogeneity

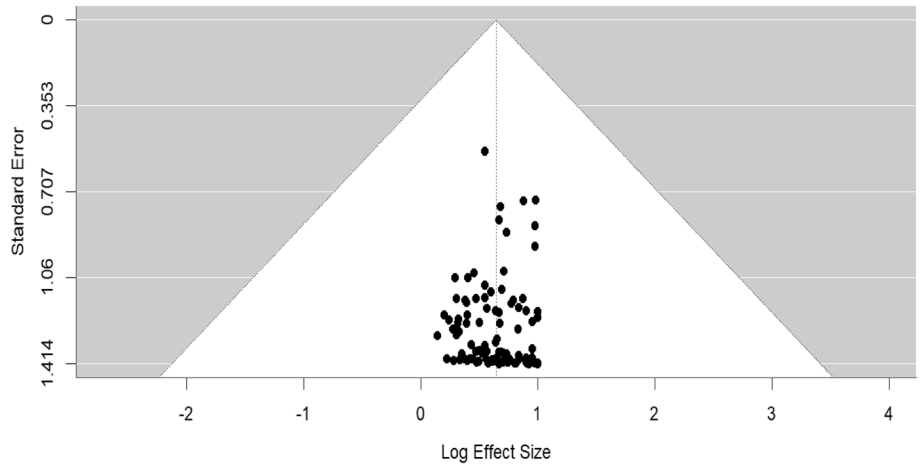

Fig. 7 Funnel plot of standard error against the log effect size

regions, similar to our findings on the effectiveness of various VRIs.

Research on the long-term safety and efficacy of a dengue vaccine in regions of endemic disease revealed a significant reduction in dengue cases among vaccinated individuals, aligning with our results that indicate substantial impact on disease prevention in high-risk areas [14]. Furthermore, a study on the efficacy and immunogenicity of a high-dose influenza vaccine in older adults found higher protection rates compared to standard-dose vaccines, supporting our findings that certain vaccine delivery methods, such as high-dose formulations, can enhance vaccine efficacy [15]. Noman et al., conducted a rapid overview of reviews to identify effective interventions for increasing vaccination rates in vulnerable groups, highlighting the importance of tailored strategies to improve immunization coverage, which is consistent with our conclusion that targeted interventions can significantly enhance vaccine efficacy [16]. Similarly, Siddiqui et al., performed a meta-analysis to assess interventions aimed at improving immunization coverage among children and adolescents, finding that community-based interventions and reminder-recall systems significantly increased vaccination rates, supporting our findings on the effectiveness of various VRIs [17].

The findings from this study and the comparison with other relevant studies have significant implications for

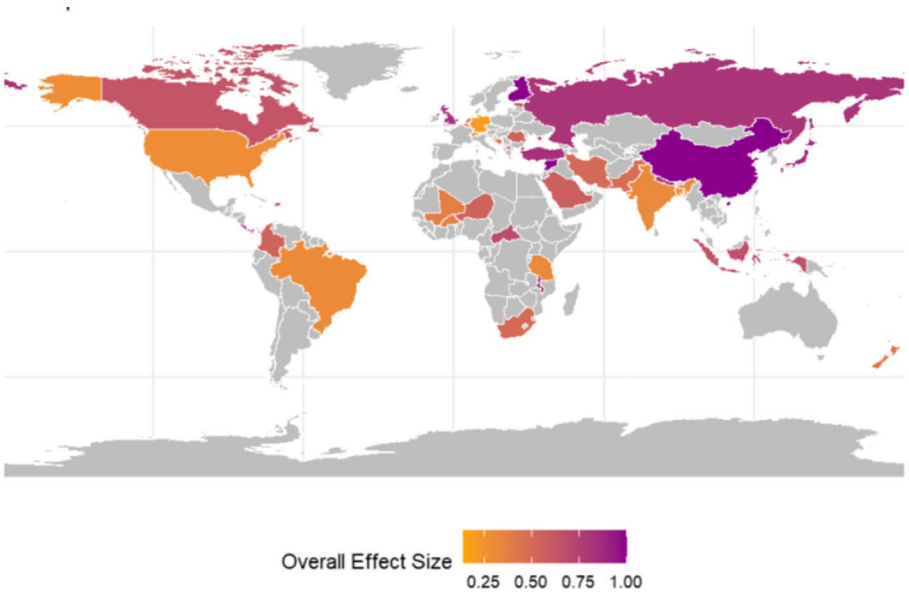

Fig. 8 Heat map showing the overall effect size based on geographic location

Table 2 Summary of year-wise meta-analysis of studies

Year	No. of studies	Effect size estimate
2015	12	0.739
2016	10	0.690
2017	15	0.508
2018	12	0.658
2019	10	0.673
2020	10	0.673
2021	31	0.719
2022	28	0.641
2023	11	0.588

$\tau^2 = 0$, $I^2 = 0.00\%$, $H^2 = 1.00$

vaccination policy. The high efficacy of mRNA-based vaccines and other targeted interventions underscores the need for incorporating these vaccines into national immunization programs. The CDC's extensive vaccine effectiveness studies provide robust evidence to inform COVID-19 vaccine policy, ensuring timely and effective vaccination strategies. Additionally, tailored interventions to increase vaccination rates in vulnerable groups and community-based strategies to improve immunization coverage among children and adolescents offer valuable insights for policymakers to design targeted vaccination campaigns. Overall, the consistent and significant positive effects of vaccine-related interventions across diverse populations and settings highlight the critical role of vaccination in public health strategies aimed at disease prevention and control. These findings support the need for continuous evaluation and adaptation of vaccination policies to address emerging health threats and improve overall vaccine coverage, ultimately leading to better health outcomes and enhanced preparedness for future infectious disease challenges. Future research should prioritize optimizing vaccine dosages and scheduling to improve efficacy, especially for new and emerging vaccines. Additionally, improvements in storage and distribution, particularly for vaccines requiring cold chain logistics, are essential to maintain their efficacy,

Table 3 Effect size based on mode of vaccine delivery

Delivery mode of intervention	Infection rate in intervention group		Infection rate in control group		Effect size	
	Mean	SD	Mean	SD	Mean	SD
Intramuscular injection	0.217	0.395	0.869	2.55	0.659	0.245
Intranasal administration	0.0757	0.107	0.110	0.142	0.394	0.200
Oral administration	0.627	1.26	1.54	3.18	0.544	0.123
Subcutaneous injection	0.208	0.387	1.01	1.40	0.760	0.149

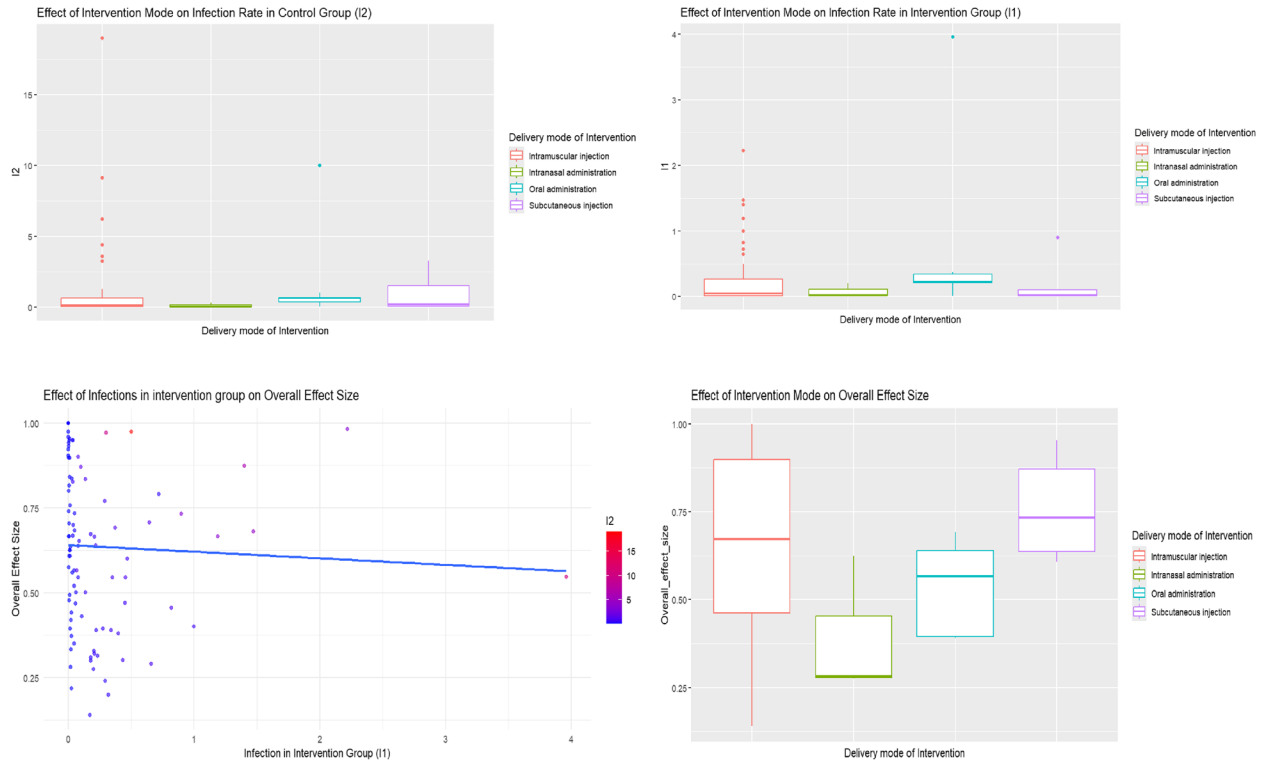

Fig. 9 Effect of delivery mode of intervention on control group, intervention group, and overall effect size

until administration. It is also crucial to continue evaluating vaccine efficacy against emerging variants of concern to ensure long-term effectiveness. Studies should explore the potential of combination vaccines to enhance protection and streamline immunization schedules. Furthermore, further investigation is needed into the necessity and timing of booster shots to sustain immunity, particularly for vaccines with waning efficacy overtime.

Conclusion

This comprehensive systematic review and meta-analysis on vaccine effectiveness presents a nuanced and detailed picture of the current state of vaccination interventions. The study's findings robustly demonstrate the high efficacy of vaccines in significantly reducing infection rates across diverse populations and settings. Vaccinated individuals exhibited remarkably lower infection rates in contrast to the non-vaccinated population. This substantial difference underscores the critical role of vaccination in public health strategies aimed at disease prevention and control.

A key strength of this meta-analysis lies in the consistency of its findings across a wide array of studies, encompassing various methodologies, population, and intervention types. This uniformity in results, characterized by an absence of significant heterogeneity, provides a high degree of confidence in the generalizability and effectiveness of vaccination interventions across different contexts. Such consistency is particularly valuable for policymakers and health practitioners, offering a solid foundation for decision-making in vaccine implementation strategies.

The study's examination of diverse vaccine delivery methods yielded important insights. Oral administration and intradermal injection methods showed particularly promising results, demonstrating high median effect sizes and lower variability in outcomes. In contrast, intramuscular and subcutaneous injections, as well as mass vaccination campaigns, exhibited greater variability in their effectiveness. This variability highlights the influence of factors such as practitioner skill, population demographics, and logistical execution on the overall success of vaccination programs.

The study emphasizes several critical areas for further research and development. These include optimizing dosages and schedules for new and emerging vaccines to enhance their efficacy, improving storage and distribution methods (particularly for vaccines requiring cold chain management), and continuously evaluating vaccine efficacy against emerging variants of concern. The exploration of combination vaccines to potentially broaden protection and streamline immunization schedules is also highlighted

as a promising area for investigation. Additionally, the study underscores the importance of research into the necessity and optimal timing of booster shots, especially for vaccines that may show waning efficacy over time.

However, the study also illuminates the complexities and challenges in vaccine implementation, particularly in the face of evolving pathogens and diverse population needs. The recommendations for future research provide a clear roadmap for addressing these challenges, emphasizing the need for continued innovation in vaccine development, delivery, and policy. By focusing on these key areas, the scientific and public health communities can work towards further improving vaccination strategies, ultimately leading to better health outcomes and enhanced preparedness for future infectious disease challenges.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-025-02856-6.

Additional file 1. Search strategy using the different databases.

Additional file 2. Study characteristics of included articles [18–152].

Additional file 3. Link for 3D MAP.

Additional file 4. Link for 3D scatter plot.

Additional file 5. Risk of bias assessment for the studies to be included in meta-analysis.

Additional file 6. Year wise summary of forest plot for the studies included in meta-analysis.

Authors' contributions

AK was responsible for the conceptualization, study design, project administration, supervision, risk of bias assessment, and critical revision of the manuscript. AK also led the data analysis. AW contributed to the development of the search strategy, methodology, PROSPERO registration, and took part in manuscript drafting and review. AR and LG carried out the primary and secondary screenings, including abstract screening and duplicate removal. LG drafted the introduction, while AR contributed significantly to manuscript writing and was responsible for referencing and preparing the reference list. HS critically reviewed and evaluated each included study, supported the validation of findings, and contributed to the manuscript writing. SM, KS, and MP were responsible for proofreading and cross-verifying the entire review process from the beginning, which led to significant corrections and improvements in the manuscript. All authors read and approved the final version of the manuscript.

Declarations

Competing interests

The authors declare that they have no competing interests.

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