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Reactogenicity of Covid–19 Boosters : A Systematic Review and Meta Analysis

JHULIA ANNA QUITAN
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Location of the practicum:
Sanofi
Lyon, France

Professional advisor:
Joshua Nealon
Sanofi

Academic advisor:
Dr. Tiffany Harris
Mailman School of Public Health
Columbia University

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List of Acronyms

Acronym / Term	Full Term / Description
COVID-19	Coronavirus Disease 2019
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
ARDS	Acute Respiratory Distress Syndrome
WHO	World Health Organization
CDC	Centers for Disease Control and Prevention
IL-1	Interleukin-1
IL-6	Interleukin-6
TNF-α	Tumor Necrosis Factor alpha
KFF	Kaiser Family Foundation
RCT	Randomized Controlled Trial
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PICO	Population, Intervention, Comparator, and Outcomes
RoB 2	Risk of Bias 2 (Cochrane Risk of Bias tool version 2)
MeSH	Medical Subject Headings
UAE	United Arab Emirates
OR	Odds Ratio
CI	Confidence Interval
ECDC	European Centre for Disease Prevention and Control
BBIBP-CorV	Beijing Institute of Biological Products COVID-19 Vaccine (inactivated)
Ad26.COV2.S	Johnson & Johnson (Janssen) COVID-19 Vaccine (viral vector)
AIC	Akaike Information Criterion
mRNA	Messenger Ribonucleic Acid
BNT162b2	Pfizer-BioNTech COVID-19 Vaccine (Comirnaty)
mRNA-1273	Moderna COVID-19 Vaccine
Novavax	Protein subunit COVID-19 vaccine developed by Novavax (NVX-CoV2373)
ChAdOx1 nCoV-19	COVID-19 Vaccine developed by Oxford/AstraZeneca using a chimpanzee adenoviral vector
AstraZeneca	Common name for the ChAdOx1 nCoV-19 viral vector vaccine

Abstract

Introduction:

COVID-19 booster vaccines play a vital role in protecting against severe illness caused by SARS-CoV-2. However, concerns about side effects, especially fever, have reduced public willingness to receive booster doses. Fever is a common immune response after vaccination and is often used as a marker of vaccine reactogenicity. This study aimed to measure how often fever occurs after booster vaccination and to identify factors that affect this risk.

Methods:

A systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted. Studies published between 2021 and 2025 were identified from PubMed, Embase, and Google Scholar. Eligible studies involved adults who received third or fourth doses of mRNA (Moderna, Pfizer), protein subunit (Novavax), or viral vector (AstraZeneca) vaccines. A random-effects meta-analysis was used to estimate pooled fever incidence. Meta-regression explored the effects of vaccine platform, dose schedule, booster type, and age group.

Results:

Fifteen RCTs including 3,548 participants were analyzed. The overall incidence of fever after booster vaccination was 7% (95% CI: 5%–11%). Fever was most common after Moderna Dose 3 and lowest after Novavax Dose 4. Meta-regression showed significantly reduced odds of fever with protein-based vaccines and fourth doses. No statistically significant differences were found for booster type (homologous vs. heterologous) or age group.

Conclusion:

This review shows that fever after COVID-19 booster vaccination is uncommon and varies by vaccine platform and dose number. Protein-based vaccines are associated with lower fever risk, making them suitable for populations sensitive to vaccine side effects. These findings can inform public health communication, guide vaccine policy, and support ongoing booster campaigns. Continued safety monitoring and updated evidence will be key to maintaining vaccine confidence.

Keywords: COVID-19 vaccine, booster dose, fever, reactogenicity, meta-analysis

Chapter 1 : Introduction

1.1 Background

COVID-19 is a contagious respiratory illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The virus spreads primarily through respiratory droplets and aerosols and can cause a wide range of symptoms, including fever, cough, fatigue, muscle aches, sore throat, and loss of taste or smell [2]. In severe cases, it can progress to pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure, and death [3].

As of 2025, COVID-19 remains endemic, with periodic surges driven by emerging viral variants. Between April 14 and May 11, 2025, over 91,000 new cases were reported across 91 countries [4]. To maintain protection against severe disease and transmission, health authorities have recommended regular booster vaccinations [5]. However, booster uptake has been declining. For instance, in the United States, fewer than 25% of eligible individuals received a COVID-19 booster in the 2024–2025 season, with uptake as low as 10% among children under age 12 years and approximately 50% among adults over 75 [6].

Multiple factors contribute to the low uptake of booster vaccines. These include vaccine fatigue, skepticism, and declining perceived risk, particularly among the young and previously infected individuals, and persistent safety concerns [7,8,9,10,11]. Adding to these issues are reduced government funding for vaccination, shifting health priorities, and logistical hurdles in vaccine delivery [12, 13].

Despite these challenges, vaccination remains an important part of controlling the remaining burden of COVID-19 diseases. Vaccination substantially lowers the risk of severe illness, hospitalization, and death, especially in high-risk groups such as the elderly and those with underlying medical conditions [14, 15, 16]. Vaccination also reduces the burden on healthcare systems, which supports broader public health resilience. [14, 15, 16]

Although the safety of COVID-19 vaccines has been well established through clinical trials and global safety monitoring, serious adverse events are very rare and are continuously monitored by major health authorities, including the World Health Organization (WHO) and the United States Centers for Disease Control and Prevention (CDC) [17, 18, 19]. However, some public

concern remains because of side effects, such as arm pain, fatigue, or fever, which are typically mild and short-lived [8].

One important aspect of vaccine safety that continues to gain attention is reactogenicity, which is the expected short-term immune responses that occur after vaccination. These effects are caused by the innate immune system, which recognizes vaccine components such as antigens or adjuvants and then releases cytokines such as IL-1, IL-6, and TNF-α to coordinate a response [21,22,23,24]. Although typically mild and transient, post-vaccination symptoms such as fever or fatigue may be misinterpreted as indicators of illness, particularly because they resemble symptoms associated with the disease the vaccine is intended to prevent. These adverse effects, while not clinically concerning, can disrupt daily activities and, if not properly understood, may contribute to increased vaccine hesitancy among the population [25, 26, 27].

Recent national surveys indicate that concerns about side effects remain a leading reason for delaying or avoiding COVID-19 booster vaccination. According to the Kaiser Family Foundation (KFF) COVID-19 Vaccine Monitor, many adults, particularly those under age 50 report fear of side effects as one of the primary factors contributing to low booster uptake, with fewer than 25% receiving the updated 2024–2025 vaccine [28]. Although clinical data show that such effects are common and typically mild, misperceptions about their severity may influence public trust [16,19]. This makes it important to evaluate and communicate reactogenicity clearly, particularly for visible outcomes like fever, which are commonly used as proxies for systemic immune response [20].

1.2 Rationale

While earlier systematic reviews, such as San Francisco Ramos et al. (2024), have evaluated the reactogenicity of COVID-19 vaccine boosters, they were limited to studies published up to early 2022 and did not fully capture the growing number of evidence from more recent trials (29). Since then, additional randomized controlled trials have been published, including studies conducted through 2025, offering updated insights into the safety and tolerability of booster doses using original vaccine platforms [30,31].

This review includes a broader and more recent set of studies, including one evaluating a bivalent COVID-19 vaccine, but primarily focuses on the reactogenicity of vaccine platforms including mRNA, protein subunit, and viral vector which continue to be widely used in many countries [31, 32]. Including these newer trials is essential to ensure that systematic reviews

reflect the most current safety data, account for evolving population immunity, and support evidence-based public health recommendations [33,34].

Fever was selected as the primary outcome for assessing reactogenicity in this review because of its biological relevance, objectivity, and is consistently reported in clinical trials (21). Fever is a well-established marker of innate immune activation, triggered by cytokines such as IL-1, IL-6, and TNF-α, which act on the hypothalamus to raise the body's temperature (35). Unlike subjective symptoms such as fatigue or headache, fever can be measured quantitatively using standardized measures, making it a reliable and comparable endpoint across studies (35).

Further, fever is among the most reported and concerning post-vaccination experiences and can shape public perceptions of vaccine safety. According to CDC, fever, headache, and fatigue are the primary side effects experienced after COVID-19 vaccination [37]. In population surveys, parents of young children and unvaccinated adults report concerns about side effects including fever as the key reason for delaying or avoiding vaccination [28].

This review also applies meta-regression techniques to examine how factors such as vaccine platform, dosing schedule, and demographic characteristics influence fever outcomes [21,29,41, 42]. Because of the continued global use of these vaccines and persistent concerns about side effects, this updated synthesis offers timely, evidence-based insights to support public health decision-making, enhance vaccine communication strategies, and address ongoing vaccine hesitancy.

1.3 Objectives of the Study

This study aims to address gaps in the current understanding of post-vaccination reactogenicity, with a specific focus on fever as a measurable and meaningful outcome. The objectives are as follows:

1. To estimate the frequency of post-vaccination fever across different COVID-19 vaccine platforms (mRNA, protein subunit, and viral vector) and among various population subgroups.
2. To identify and quantify the determinants of fever by examining demographic (e.g., age, sex), clinical (e.g., comorbidities), and vaccine-related (e.g., dose number, vaccine type) factors associated with reactogenicity, using meta-regression analysis.

3. To assess the public health implications of vaccine-induced fever, particularly in relation to vaccine acceptance, risk communication strategies, and policymaking aimed at improving vaccine uptake and public confidence.

Chapter 2: Methods

2.1 Study Design

This study is a systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating the reactogenicity of COVID-19 vaccine booster doses. It follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure transparency and reproducibility.

2.2 Eligibility Criteria

The inclusion of studies in this review was guided by the Population, Intervention, Comparator, and Outcomes (PICO) framework, which systematically considers each factor relevant to the research objectives (Table 1).

Population	Individuals aged 18 years and older.
Intervention	Full-dose COVID-19 vaccines boosters (Dose 3 and Dose 4) • Moderna (mRNA 1273) • Pfizer-BioNTech (BNT162b2) • Novavax (Protein) • AstraZeneca (Viral Vector)
Comparators	NA – meta-analysis of proportions
Outcomes	Proportion of participants experiencing Fever assessed within 7 days post-vaccination
Study Design	Randomized Controlled Trials Phase II to IV conducted between 2021 and 2025

Table 1 PICO framework for inclusion of studies

Only studies published in English were considered for inclusion in this review. Studies were excluded if they met any of the following criteria:

- **Population:** Pregnant women, immunocompromised individuals, or participants with specific underlying medical conditions.
- **Intervention:** Studies in which participants received a COVID-19 vaccine concurrently with another vaccine (e.g., influenza vaccine), used non-standard routes of administration (such as intradermal injection), or involved incomplete dosing (e.g., fractional doses).
- **Outcomes:** Did not report the proportion of participants experiencing reactogenicity or failed to mention adverse events in the abstract.
- **Study Type:** Comprised interim analyses, health economic evaluations, case reports, or lacked primary data on vaccine reactogenicity

2.3 Database and Search Terms

A comprehensive literature search was conducted across three major databases: PubMed, Embase, and Google Scholar. The search strategy was structured using the PICO framework and implemented with Boolean operators (AND, OR, NOT) to systematically combine search terms and refine results. To enhance precision and consistency, the search included both Medical Subject Headings (MeSH) and free-text synonyms. These methods are widely recommended in systematic review methodology to ensure comprehensive and reproducible evidence retrieval [43,44].

Search terms covered key concepts such as COVID-19, vaccine names, safety, and reactogenicity, with filters applied for study design and population. A detailed breakdown of the search logic for each database is provided in Appendix A.

2.4 Selection of Studies

The search results were imported into Covidence, a web application for systematic reviews (45). After removing duplicate records, titles and abstracts were screened. Each record was independently reviewed by two members of the study team, and those that did not meet the inclusion criteria were excluded.

Articles were deemed suitable for inclusion if they described a randomized clinical trial of a COVID-19 vaccine booster (Phase II to IV of clinical development), included participants who

had previously received an approved COVID-19 primary vaccine regimen, and assessed safety or reactogenicity.

Abstracts were excluded if they described non-randomized studies, preprints or protocol-only articles, primary COVID-19 vaccine schedules, vaccines not administered intramuscularly, co-administration of COVID-19 vaccines with other vaccines, and trials where safety data were not reported.

Full-text articles were retrieved for every abstract included during the initial screening phase. The same two authors assessed the full-text articles and excluded those that did not meet the eligibility criteria. Disagreements were resolved by consensus between the two reviewers. Reference lists of included articles were also reviewed to identify additional studies that met the eligibility criteria.

2.5 Risk of Bias Assessment

The risk of bias for each included randomized controlled trial was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool [66]. This evaluation covered five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. The assessment was conducted using R, with a custom script developed to extract relevant study-level data and populate the RoB 2 template. This approach ensured consistency and reproducibility in the evaluation process. Preliminary judgments were assigned based on available metadata, and the resulting RoB table was reviewed for completeness and accuracy. Detailed risk of bias ratings for each study is presented in Appendix B.

2.6 Data Extraction

Data were extracted from eligible RCTs identified through the systematic literature search. The extraction focused only on participants who received a third or fourth dose of a COVID-19 vaccine. Comparator groups (e.g., placebo or alternative vaccine recipients) were excluded. This approach allowed for estimating the absolute incidence of fever across vaccine platforms and dose schedules.

2.6.1 Primary Outcome Selection

Fever was selected as the primary reactogenicity outcome due to its biological relevance, objective measurement, and consistent reporting across clinical trials. Unlike subjective symptoms such as fatigue or headache, fever is defined by standardized temperature thresholds [100.4 °F (38 °C) or greater] and serves as a quantifiable marker of systemic immune activation, which is a central goal of booster vaccination programs [39,20].

2.6.2 Extracted Outcome Variables

For each study and dose group, the following outcome data were extracted:

- Total sample size per dose
- Number of participants reporting fever
- Percentage of participants reporting fever

When only percentages were reported, the number of participants experiencing fever was estimated using the formula:

Number of events = (% Events ÷ 100) × Total sample size per dose

If dose-specific sample sizes were not available, the overall study sample size was used as a proxy. This method ensured inclusion of studies that reported outcomes only at the trial level while preserving analytical consistency across pooled analyses [43].

2.6.3 Extracted Covariates

To enable subgroup analysis and meta-regression, the following study-level covariates were extracted, selected based on prior literature and biological plausibility:

- **Vaccine platform** (mRNA, protein subunit, or viral vector): Different platforms engage immune responses to varying degrees due to differences in antigen delivery and innate immune stimulation [29, 31,41,42,].
- **Dose schedule** (Dose 3 vs. Dose 4): Reactogenicity may vary with repeated exposure, possibly decreasing due to immune adaptation or tolerance [33].
- **Booster type** (homologous vs. heterologous): Mixing vaccine platforms may affect immunogenicity and side-effect profiles [30,35,41].
- **Age group** (e.g., 18–44, 45–64, 65+): Younger adults may exhibit stronger systemic responses due to more robust immune activation [20,31,41].

- **Country** (e.g., USA, UK, Australia): Country was included to capture differences in vaccine deployment strategies, background immunity, safety reporting systems, and sociocultural perceptions of side effects, all of which may influence reactogenicity outcomes [5,6,29,31].

These covariates were consistently reported across studies and used in stratified and multivariable analyses to explore heterogeneity in fever incidence. Gender was not included as a covariate because it was not consistently reported across studies, limiting its usefulness for comparative subgroup analysis [29]

2.7 Statistical Analysis

2.7.1 Meta-Analysis

Descriptive statistics summarized study characteristics using frequencies and ranges. A random-effects meta-analysis was performed using the metafor package in R [47], applying logit-transformed proportions to stabilize variance and accommodate extreme values [48]. This method is suited for analyzing single-arm binary outcomes like fever incidence, especially when comparing across heterogeneous study populations [49].

Between-study heterogeneity was assessed using the I^2 statistic, with thresholds of 25%, 50%, and 75% interpreted as low, moderate, and high heterogeneity, respectively [49]. Forest plots were generated to visualize the pooled incidence and confidence intervals.

Stratified Analyses

Meta-analyses were stratified by:

- Vaccine platform (mRNA-1273, BNT162b2, Protein, Viral Vector)
- Dose schedule (Dose 3 vs. Dose 4)

Stratification will enable to study potential differences in fever incidence across vaccine platforms and dosing intervals, while also accounting for demographic and geographical or related factors [29, 31, 41, 42].

2.7.2 Meta-Regression

To explore sources of heterogeneity, a multivariable random-effects meta-regression was conducted using the rma() function in the metafor package [47]. Covariates were selected using

backward stepwise elimination based on Akaike Information Criterion (AIC) to identify the most parsimonious model [64,65].

- Vaccine platform (reference: mRNA-1273)
- Dose schedule (reference: Dose 3)
- Booster type (reference: Homologous)
- Age group (reference: 18–44 years)
- Country (reference: USA)

Logit transformation ensured that the model's predictions remained bounded and statistically stable [48]. Although fever is a common post-vaccination reaction, its reported incidence in the included studies was generally low (1%–10%). Odds ratios (ORs) derived from logit-transformed meta-regression models were used because this is a valid measure and can approximate risk ratios under such conditions [47, 48]. Meta-regression results reflect between-study associations, which are appropriate for single-arm analyses and align with established guidelines for meta-regression of binary outcomes [49].

Chapter 3 : Results

3.1 Literature Search and Risk of Bias

The three databases were searched from February 17, 2025 to April 15, 2025 and produced 1410 results. After duplicates were removed, 1404 articles were screened. A total of fourteen studies that describe the 4 major vaccine types mRNA 1273, BNT162b2, Protein and Viral Vector met the inclusion criteria for the systematic review and underwent RoB assessment. Most of the studies were deemed to have low RoB while four had some concerns. The PRISMA flow diagram is presented in Figure 1.

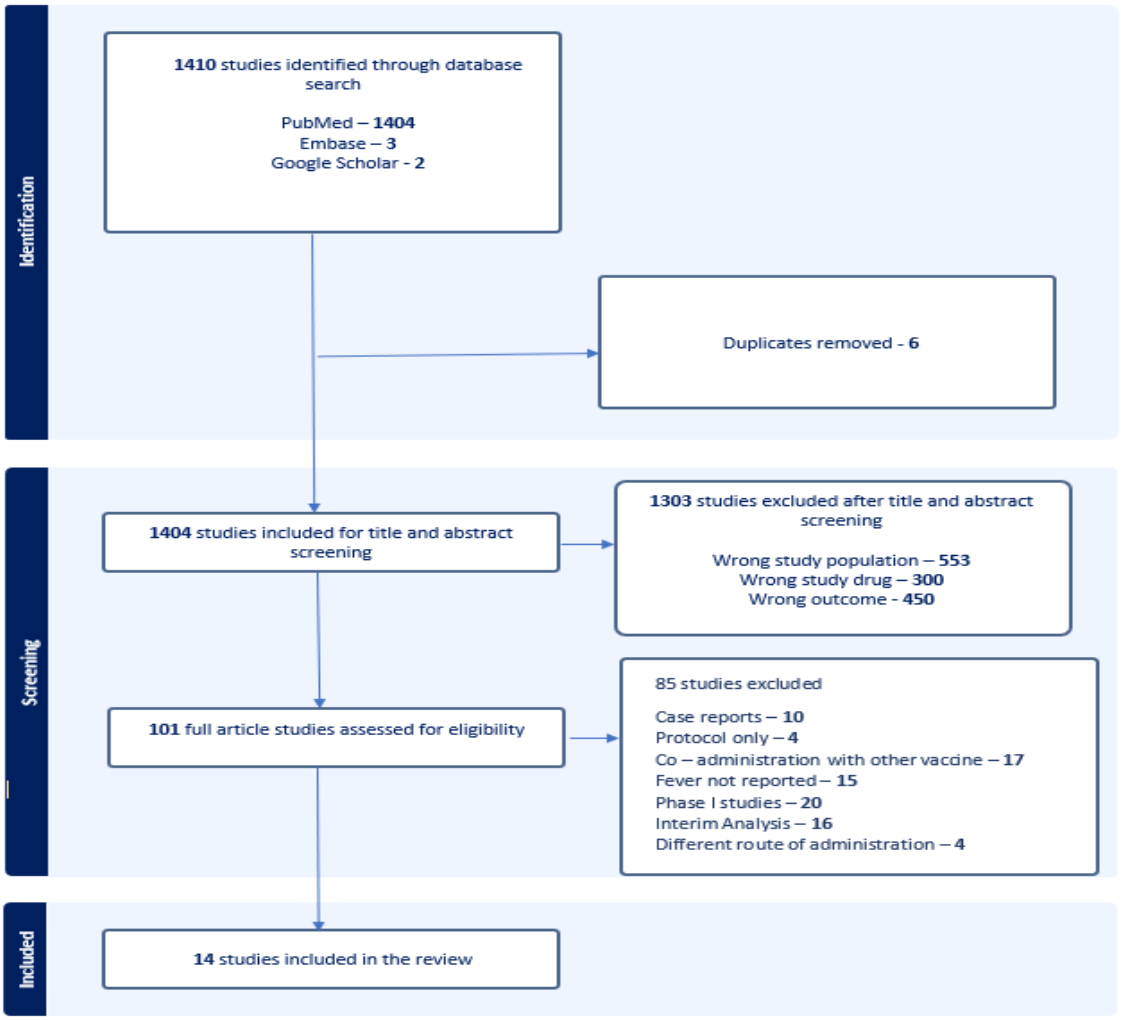

Figure 1: Prisma Flow Diagram
Diagram downloaded from Covidence App

3.2 Systematic Review

Fourteen randomized controlled trials evaluating the safety and reactogenicity of COVID-19 booster vaccinations were included in this systematic review, comprised with a total of 3,398 participants. These trials assessed the incidence of fever following administration of booster doses from four vaccine platforms: mRNA [Moderna (mRNA-1273), Pfizer (BNT162b2], protein-based (Novavax), and viral vector (AstraZeneca) vaccines. Booster doses were administered either as a third (Dose 3) or fourth (Dose 4) dose.

The most frequently studied vaccine was Pfizer [BNT162b2 (8 studies)], followed by Novavax (protein) and Moderna (mRNA-1273) with 6 studies each, and AstraZeneca [viral vector (2 studies)]. Several trials included multiple vaccine arms, allowing comparisons within a single study population. Booster configurations varied, with most participants receiving their booster after a primary series of AstraZeneca (viral vector) [53, 54,55,60] Novavax (protein) [51,58],Pfizer (BNT162b2) [52,60] or Moderna (mRNA 1273) [52,61]. A few studies included heterologous primary regimens or less commonly used vaccines such as CoronaVac, Ad26.COV2.S, and BBIBP-CorV [56,57,62,63]. Two studies administered Dose 4 to participants who had received any type of three prior COVID-19 vaccine doses [33, 59] .

Participants ranged in age from 18 to over 80 years. While most studies enrolled healthy adults aged 18 and older, some focused on specific age groups, such as 30–80 years or 50 years and above. The median age range across studies was approximately 25 to 65 years. Female representation ranged from 15.3% to 75.5%, with most studies having a balanced number of males and females. One study from the UAE [63] had a lower proportion of female participants. A table for study characteristics is presented in Table 1.

The trials were geographically diverse, covering WHO regions including the Americas (USA, Brazil), Europe (Spain, United Kingdom, Netherlands), the Western Pacific (Japan, Taiwan, Hong Kong), and the Eastern Mediterranean (UAE). No studies were conducted in the African Region or other Eastern Mediterranean countries outside of the UAE. A map of included countries is provided in Figure 2.

Study (Author, Year)	Country	Sample Size	Vaccine	Dose Schedule	Primary Covid 19 Vaccine	Age Range	Percentage Females (%)
Alves 2023	USA	150,	Novavax	Dose 3, Dose 4	2 doses of Novavax, 3 doses of Novavax	18 - 84	52.2,
Bennett 2024	Australia	274	Novavax	Dose 4	3 doses of Moderna or Pfizer	18 - 64	52.2
Borobia 2021	Spain	450	Pfizer	Dose 3	2 doses of AstraZeneca	18 - 60	57.1
Chen 2022	Taiwan	50	AstraZeneca	Dose 3	2 doses of AstraZeneca	24 - 62	52
Chuang 2022	Taiwan	168,	Moderna, Pfizer	Dose 3	2 doses of AstraZeneca	20 - 65	67.3,
CostaClemens 2023	Brazil	231	AstraZeneca	Dose 3	2 doses of CoronaVac	18 - 81	45.6
LeungNHL 2023	Hongkong	114	Pfizer	Dose 3	2 doses of CoronoVac or Pfizer	18 - 79	51
Marchese 2025	United Kingdom	325,	Pfizer, Moderna, Novavax	Dose 3	2 doses of Astrazeneca or Pfizer	30 - 80	58.2,
Mazarakis 2025	Australia	353,	Moderna, Novavax	Dose 4	3 doses of any Covid - 19 Vaccine	25 - 43	69.1,
McLeod 2024	Australia	117,	Moderna, Novavax, Pfizer	Dose 4	3 doses of any Covid 19 Vaccine	50 - <70	75.5,
MunroAPS 2022	United Kingdom	83	Pfizer	Dose 4	2 doses of Astrazeneca or Pfizer and 1 dose booster of Pfizer	30 - 80	50.6
Oda 2024	Japan	408	Pfizer	Dose 3	2 doses of Moderna	18 - 76	58.6
SablerollesRSG 2022	Netherlands	223,	Moderna, Pfizer	Dose 3	2 doses of Ad26.CoV2.S	31 - 49, 29 - 47	63.2,
Toback 2024	UAE	497	Novavax	Dose 3	2 doses of BBIBP-CorV	18 - 56	15.3

Table 1: Characteristics of Studies Included in the Review

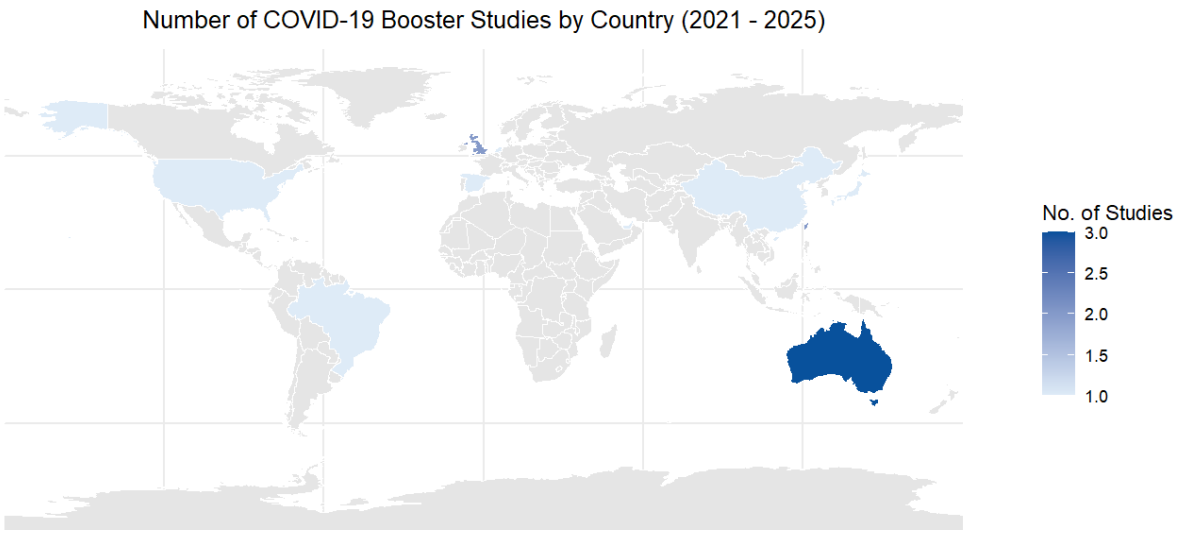

Figure 2: Number of studies included per Country
Map generated using R with packages (ggplot2) and (rnaturalearth)

3.3 Meta Analysis

A random-effects meta-analysis was conducted using logit-transformed proportions to estimate the pooled proportion of participants who experienced fever after COVID-19 booster vaccination [48]. The results are presented in a forest plot (Figure 3).

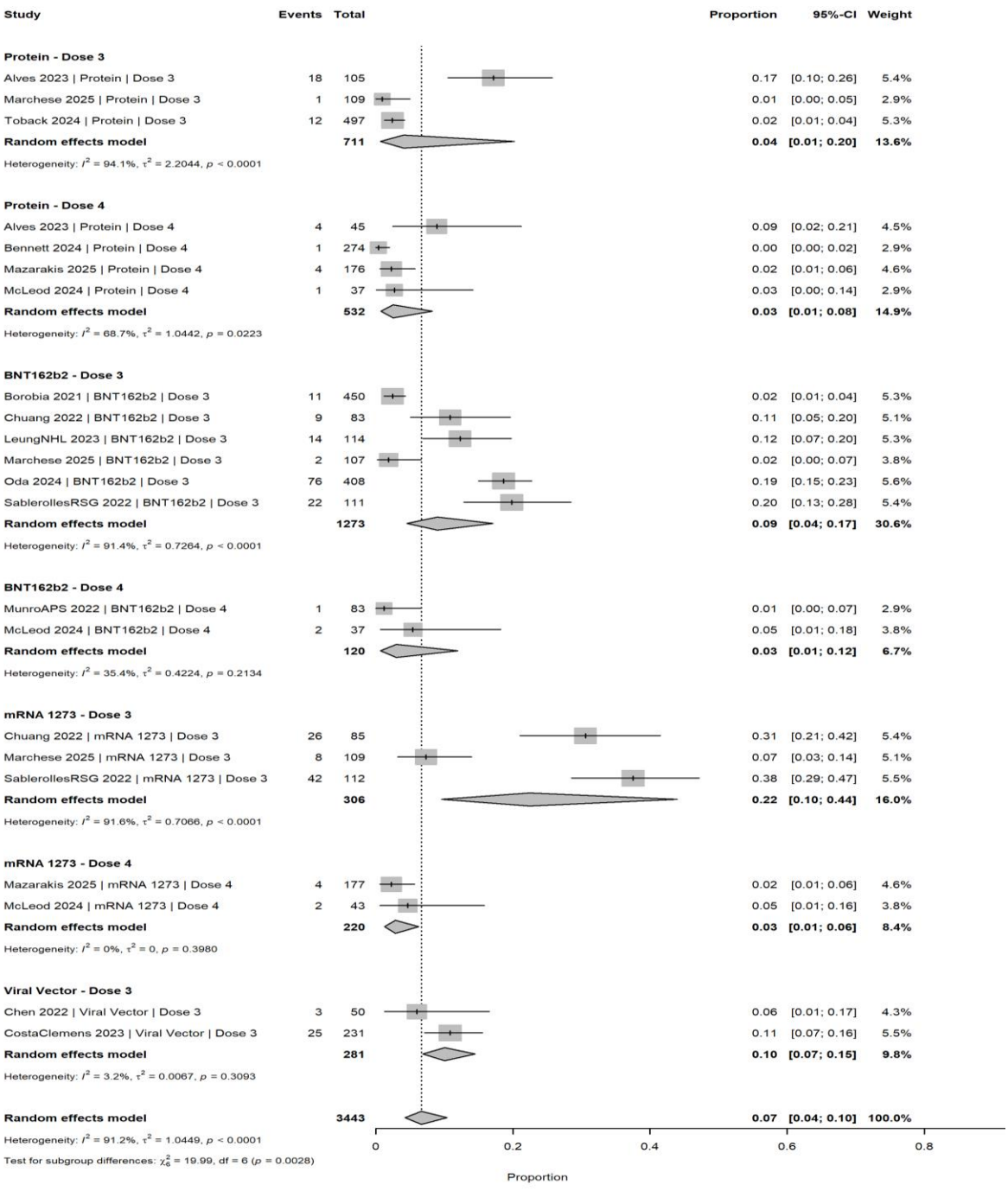

Figure 3: Forest Plot of Fever Stratified by Vaccine Type and Dose Schedule
Plot generated using R

Fourteen randomized controlled trials were included in the meta-analysis evaluating fever incidence after COVID-19 booster vaccination. The overall pooled incidence of fever was 7% (95% CI: 4%–10%), with substantial between-study heterogeneity of 91.2% [49]. A test for subgroup differences was statistically significant (p value 0.0028) [64], indicating that fever incidence varied significantly by vaccine platform and dose schedule [29].

When stratified by vaccine type and dose, notable differences were observed. For protein-based vaccines, the pooled fever incidence was 4% (95% CI: 1%–20%) after Dose 3 and decreased to 3% (95% CI: 1%–8%) after Dose 4. BNT162b2 (Pfizer) showed a fever incidence of 9% (95% CI: 4%–17%) after Dose 3 and 3% (95% CI: 1%–12%) after Dose 4. mRNA-1273 (Moderna) had the highest incidence following Dose 3 at 22% (95% CI: 10%–44%), but this dropped to 3% (95% CI: 1%–6%) following Dose 4. For viral vector vaccines, which were only administered as Dose 3, the pooled incidence was 10% (95% CI: 7%–15%).

The heterogeneity observed within subgroups, particularly among mRNA- and protein-based vaccines, suggests variability in study populations or vaccine formulations. Because of these differences, further investigation using multivariable meta-regression is aimed at identifying study-level predictors of fever reactogenicity across vaccine platforms, dose schedules, and participant characteristics [31,41,50].

3.4 Meta Regression

A multivariable random-effects meta-regression was conducted to examine study-level predictors of fever incidence following COVID-19 booster vaccination. The initial model included vaccine platform, dose schedule, booster type, age group, and country. Using backward stepwise selection based on the Akaike Information Criterion (AIC), country was removed from the final model because of its high non-significant p-value and limited explanatory value. Its exclusion resulted in a more parsimonious model with improved fit and greater stability. These adjusted estimates were exponentiated to yield odds ratios (ORs) and 95% confidence intervals (CIs), as shown in Figure 4.

Meta-Regression Results: Fever Reactogenicity			
Term	Estimate (Log Odds) [95% CI]	Odds Ratio [95% CI]	p-value
intercept	0.231 [0.066, 0.396]	1.26 [1.07, 1.49]	0.006
Vaccine Group: BNT162b2 (ref = mRNA 1273)	-0.072 [-0.175, 0.031]	0.93 [0.84, 1.03]	0.171
Vaccine Group: Protein (ref = mRNA 1273)	-0.115 [-0.221, -0.009]	0.89 [0.8, 0.99]	0.033
Vaccine Group: Viral Vector (ref = mRNA 1273)	-0.134 [-0.299, 0.031]	0.87 [0.74, 1.03]	0.113
Dose Schedule: Dose 4 (ref = Dose 3)	-0.098 [-0.186, -0.009]	0.91 [0.83, 0.99]	0.031
Booster Type: Heterologous (ref = Homologous)	-0.024 [-0.156, 0.108]	0.98 [0.86, 1.11]	0.725
Age Group: Middle-aged Adults (45-64) (ref = Young Adults 18-44)	-0.001 [-0.124, 0.122]	1 [0.88, 1.13]	0.987
Age Group: Elderly (65+) (ref = Young Adults 18-44)	-0.091 [-0.207, 0.024]	0.91 [0.81, 1.02]	0.121
Both log odds and odds ratios are presented. Estimates are derived from a meta-regression model on logit-transformed proportions.			

Figure 4: Meta Regression Results Fever
Results table generated using R

Compared to mRNA-1273, the odds of fever were significantly lower for participants who received protein-based vaccines (e.g., Novavax), with an OR of 0.89 (95% CI: 0.81–0.99, p = 0.033). BNT162b2 (Pfizer) and viral vector vaccines were also associated with lower odds of fever (OR = 0.93 and 0.87, respectively), though these differences did not reach statistical significance (p = 0.171 and p = 0.113, respectively).

The odds of having a fever were considerably lower for those who got Dose 4 boosters than for those who received Dose 3 (OR = 0.91; 95% CI: 0.83–0.99; p = 0.031).

Neither booster type (heterologous vs. homologous) nor age group (middle-aged adults and elderly vs. 18–44 years) was significantly associated with the odds of fever (all p-values > 0.10). Specifically, heterologous boosting yielded an OR of 0.97 (95% CI: 0.85–1.09, p = 0.587), and elderly adults had an OR of 0.91 (95% CI: 0.82–1.02, p = 0.121) compared to young adults.

Chapter 4 : Discussion

This systematic review and meta-analysis evaluated the incidence of fever after COVID-19 booster vaccinations using data from 15 randomized controlled trials conducted across diverse geographic settings. By synthesizing findings across mRNA, protein subunit, and viral vector vaccine platforms, this study aimed to quantify reactogenicity and identify predictors of fever as an important systemic outcome. The results revealed two major findings: (1) the overall incidence of fever following booster doses was low, (2) fever incidence varied substantially by vaccine platform and dose schedule.

4.1 Comparison with Previous Literature

Our findings are consistent with previous research indicating that reactogenicity varies by vaccine platform. For example, Rousculp et al. (2024) reported that mRNA vaccines, particularly Moderna's mRNA 1273, are associated with higher rates of systemic reactogenicity, including fever, compared to protein subunit vaccines such as Novavax. These differences have been attributed to the underlying mechanisms of immunogenicity: mRNA vaccines induce strong innate immune responses through intracellular antigen translation and expression, while protein subunit vaccines deliver the antigen directly with an adjuvant that modulates the inflammatory response [65, 22, 24].

In support of this, the meta-regression conducted in our study found that Novavax was associated with significantly lower odds of fever compared to mRNA-1273 (OR = 0.89, p = 0.033). This is consistent with prior observational and clinical trial data showing reduced reactogenicity of protein subunit platforms relative to mRNA-based vaccines. For example, San Francisco et al. (2024) and McDonald et al. (2021) also found that protein-based boosters like Novavax triggered lower inflammatory responses, aligning with their adjuvanted antigen delivery mechanisms [29, 41]. Together, these findings reinforce the platform-specific differences in reactogenicity and support the observed lower fever incidence associated with protein-based COVID-19 booster vaccines.

4.2 Implications of Dose Schedule and Repeated Boosting

This study also identified a consistent reduction in fever incidence following fourth (dose 4) booster doses across all vaccine platforms. For example, fever incidence associated with mRNA-1273 declined from 22% after Dose 3 to just 3% after Dose 4. The meta-regression confirmed a statistically significant reduction in the odds of fever among Dose 4 recipients compared to Dose 3 (OR = 0.91, p = 0.031). Although not explicitly mentioned that dose 4 elicits less systemic reactogenicity including fever, Munro et al. (2022) found that 4 is well tolerated [60]. These findings suggest a possible attenuation of reactogenicity with repeated immunization, potentially due to immunological adaptation, modulation of innate immune responses, or reduced antigen novelty over time [22,23,24].

Notably, this pattern appears to reflect a broader trend across the vaccination timeline. Fever rates were highest after the primary series, particularly after Dose 2, with several studies reporting peak systemic reactogenicity, including fever, at that stage [21, 22, 31, 38, 59].

Similar patterns have been reported in recent clinical trials of fourth-dose boosters. For example, McLeod et al. (2024) observed lower rates of systemic adverse events, including fever, following a fourth dose compared to the third, regardless of vaccine platform [59]. This trend aligns with studies suggesting that repeated antigen exposure may lead to immune tolerance or a more regulated inflammatory response [21, 23].

These findings have important public health implications. Concerns about adverse events, particularly with additional booster doses, remain a leading cause of vaccine hesitancy in many populations [7, 8, 28]. Demonstrating that systemic reactogenicity, including fever, does not intensify with successive doses may help alleviate safety concerns, establish confidence in ongoing vaccination campaigns, and improve uptake of future booster doses, especially in vulnerable populations.

4.3 Role of Booster Type and Age Group

Although heterologous boosting was not significantly associated with fever in this analysis (OR = 0.98, p = 0.725), prior studies have produced mixed findings. For example, Atmar et al. (2022) reported that fever occurred in 17.3% of participants receiving a heterologous mRNA booster after priming with Ad26.COV2.S, compared to 14.1% in those receiving homologous mRNA boosters [67]. Similarly, the European Centre for Disease Prevention and Control (ECDC) noted a slight increase in systemic reactogenicity, including fever, with heterologous regimens, particularly when switching from viral vector to mRNA platforms, likely due to enhanced stimulation of the body's initial immune defenses [5]. However, our analysis may have been underpowered to detect such differences, given the heterogeneity in booster regimens and the limited number of studies directly comparing homologous versus heterologous schedules within the same trial framework.

Although no statistically significant association was found between age group and fever incidence, older adults (65+) exhibited slightly lower odds of fever compared to younger adults aged 18–44 (OR = 0.91, p = 0.121). This finding is biologically plausible and aligns with previous research suggesting that younger individuals tend to generate stronger immune responses to vaccination, which may lead to more frequent systemic side effects such as fever [68]. Hervé et al. (2019) and Pardi et al. (2022) attribute these differences to age-related changes in immune system function, specifically, a gradual weakening of immune responsiveness with age, including reduced signaling and lower levels of inflammatory cytokines [21, 22].

4.4 Strengths and Limitations

A key strength of this study is its comprehensive inclusion of randomized controlled trials published up to mid-2025, expanding on earlier reviews such as that by San Francisco Ramos et al. [29], which included data only through early 2022. This broader time frame allowed for the inclusion of more recent trials evaluating fourth booster doses and variant-adapted vaccine formulations, both of which are critical given the evolving immunization landscape and emergence of new SARS-CoV-2 variants. These updated trials reflect real-world vaccination strategies and regulatory priorities, thereby enhancing the relevance and applicability of the findings for current public health decision-making [33, 34].

Additionally, the use of logit-transformed single-arm proportions allowed for statistically valid estimation of pooled odds ratios even in the presence of low event rates [48].

However, this study has several limitations. First, despite the overall consistency in outcome reporting, variations in reactogenicity assessment methods, particularly for fever across trials may have introduced measurement bias [41]. Second, sample sizes for some key subgroups such as recipients of Dose 4 and elderly adults were relatively small, limiting statistical power to detect subgroup effects [59,60]. Third, several trials evaluated mixed vaccine platforms or heterologous booster schedules, complicating the isolation of platform-specific effects [56, 60]. Fourth, although country was initially included as a covariate in the meta-regression to account for contextual variation in vaccine rollout and surveillance systems, it was excluded from the final model due to its high p-value and limited explanatory value. Lastly, this analysis focused exclusively on fever, excluding other common systemic outcomes such as fatigue, myalgia, or headache, which may also be important indicators of reactogenicity [21,41].

4.5 Public Health Relevance

These findings emphasize the importance of tailoring vaccine communication strategies to align with the reactogenicity profiles of different vaccine platforms. For instance, protein-based vaccines such as Novavax, which were associated with the lowest fever incidence in this analysis, may be particularly suitable for populations with heightened sensitivity to vaccine side effects. This includes older adults, individuals with underlying health conditions, or those who have experienced adverse reactions to prior doses. Transparent communication about the lower reactogenicity of such platforms could improve vaccine acceptability and help address concerns that often drive hesitancy, especially in vulnerable or risk-averse groups.

Additionally, the observation that systemic side effects such as fever do not increase and may actually decrease with fourth booster doses offers reassurance that repeated immunization

does not increase discomfort or risk. This may help address public concerns about “booster fatigue” and support ongoing recommendations for periodic boosting in high-risk populations, including the elderly and immunocompromised. Emphasizing the safety of continued boosting can strengthen the case for updated vaccination strategies in the context of waning immunity and the emergence of new SARS-CoV-2 variants.

Overall, this study contributes new and timely evidence to inform global COVID-19 booster policies. By describing the reactogenicity of vaccine platforms and dose schedules, it offers actionable insights for optimizing vaccine deployment and tailoring recommendations to maximize both safety and public trust. The findings also highlight the importance of continued monitoring of post-vaccination safety, particularly as new formulations and delivery platforms are introduced. Sustained investment in surveillance and transparent risk communication will be essential to maintain public confidence and ensure high coverage in future booster campaigns.

4.6 Conclusion

This systematic review and meta-regression provide updated and comprehensive evidence on fever reactogenicity following COVID-19 booster vaccination, incorporating data from recent trials up to mid-2025. The overall pooled incidence of fever was low (7%), but significant heterogeneity was observed across studies. Fever rates varied meaningfully by vaccine platform and dose number, with protein-based vaccines such as Novavax and fourth booster doses consistently associated with reduced odds of fever. These findings support the potential utility of such vaccines and later booster doses in minimizing systemic adverse events, a critical consideration for populations with heightened sensitivity to vaccine-related symptoms.

No statistically significant differences in fever incidence were detected by booster type (homologous vs. heterologous) or age group, although trends indicated slightly lower fever odds among older adults and during heterologous boosting. These non-significant findings may reflect limitations in study power or variability in dosing combinations across trials.

Importantly, these findings have actionable implications for public health messaging, regulatory decision-making, and the optimization of booster recommendations. By demonstrating that reactogenicity does not necessarily increase with successive doses and may in fact diminish, this evidence may help mitigate concerns related to vaccine safety and support uptake of future booster programs. Continued post-market surveillance and high-quality research are needed to evaluate emerging vaccine technologies, variant-adapted formulations, and evolving population

needs. Such efforts will be essential for maintaining vaccine confidence and ensuring the long-term success of COVID-19 immunization strategies.

References

1. Centers for Disease Control and Prevention. About COVID-19. Atlanta (GA): CDC; [updated 2024 Nov 1; cited 2025 Jun 15]. Available from: https://www.cdc.gov/covid/about/index.html

2. Centers for Disease Control and Prevention. Symptoms of COVID-19. Atlanta (GA): CDC; [updated 2024 Oct 12; cited 2025 Jun 15]. Available from: https://www.cdc.gov/covid/signs-symptoms/index.html

3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708–20. doi:10.1056/NEJMoa2002032

4. World Health Organization. COVID-19 situation update: variant NB.1.8.1 under monitoring in 22 countries. Geneva: WHO; 2025 May 12 [cited 2025 Jun 15]. Available from: https://www.who.int/emergencies/disease-outbreak-news/item/2025-DON572

5. World Health Organization. COVID-19 vaccines advice. Geneva: WHO; 2024 Oct [cited 2025 Jun 15]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines/advice

6. Centers for Disease Control and Prevention. Weekly COVID-19 Vaccination Dashboard; child and adult coverage—United States, week ending April 26, 2025 [Internet]. Atlanta (GA): CDC; 2025 [cited 2025 Jun 15]. Available from: https://www.cdc.gov/covidvaxview/weekly-dashboard/index.html

7. Vecchio MG, et al. Factors associated with COVID-19 booster vaccine hesitancy. Public Health. 2023. [as referenced in a commentary].

8. Bodas M, et al. The psychology of COVID-19 booster hesitancy, acceptance and related factors. Psychol Health Med. 2023.

9. Swire-Thompson B, et al. Meeting the challenge of vaccine hesitancy: safety concerns, misinformation. Cleve Clin J Med. 2024;91(Suppl 1):S50–6.

10. Taha SA, et al. What are the reasons for refusing a COVID-19 vaccine? BMC Public Health. 2022;22:13265.

11. Kricorian K, Civen R, Equils O. COVID-19 vaccine hesitancy: misinformation and perceptions of vaccine safety. *Hum Vaccin Immunother*. 2022;18(1):1950504. doi:10.1080/21645515.2021.1950504. PMID:34325612; PMCID:PMC8920251.

12. Gavi, the Vaccine Alliance. Learning from COVID-19 to support vaccine delivery during future health emergencies. Geneva: Gavi; 2024 Jan [cited 2025 Jun 15].

13. Arnold F. Solve delivery challenges today to futureproof Africa's vaccine infrastructure. Institute for Global Change; 2022 Mar [cited 2025 Jun 15].

14. Rahmani K, Shavaleh R, Forouhi M, et al. The effectiveness of COVID-19 vaccines in reducing the incidence, hospitalization, and mortality from COVID-19: a systematic review and meta-analysis. Front Public Health. 2022; 10:873596.

15. Prasad V, Makary MA. An evidence-based approach to Covid-19 vaccination. *N Engl J Med*. 2025;390(23):e45. doi:10.1056/NEJMsb2506929

16. Centers for Disease Control and Prevention. Benefits of getting vaccinated | COVID-19. Atlanta (GA): CDC; 2025 Jun [cited 2025 Jun 15]. Available from: https://www.cdc.gov/covid/vaccines/benefits.html

17. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19) vaccine safety. Atlanta (GA): CDC; 2025 [cited 2025 Jun 15].

18. Rzymski P, Eamsobhana P, Fal A, et al. Global safety monitoring of COVID-19 vaccines: challenges, preparations, and outlooks. Drug Saf. 2022;45(10):963–75.

19. Centers for Disease Control and Prevention. *Benefits of getting vaccinated* [Internet]. Atlanta: CDC; 2025 [cited 2025 Jun 15]. Available from: https://www.cdc.gov/covid/vaccines/benefits.html

20. Miller E, Wodi AP. Chapter 2: General best practice guidance for immunization. In: *Epidemiology and Prevention of Vaccine-Preventable Diseases* [Internet]. 14th ed. Atlanta: Centers for Disease Control and Prevention; 2021 [cited 2025 Jun 15]. Available from: https://www.cdc.gov/pinkbook/hcp/table-of-contents/chapter-2-general-best-practice-guidance.html

21.Hervé C, Laupèze B, Del Giudice G, Didierlaurent A, Da Silva F. The how's and what's of vaccine reactogenicity. NPJ Vaccines. 2019;4:39.

22. Pardi N, Hogan MJ, Porter FW, Weissman D. Innate immune mechanisms of mRNA vaccines. Nat Rev Immunol. 2022;22(4):211–29.

23. Zhang Y, Harshbarger R, Yang W. Innate responses to COVID-19 mRNA vaccines—focus on cytokine induction. Front Immunol. 2023;14:975363.

24. Didierlaurent A, Laupèze B. Vaccine adjuvants: mechanisms and platforms. Nat Rev Immunol. 2022;23(7):401–19.

25. Dinarello CA. A guide to IL-1 family cytokines in adjuvanticity. FEBS J. 2014;281(8):1859–

26. Haque N, Rahman M, Kalil AC. Side effects of COVID-19 vaccines and perceptions about COVID-19 in Bangladesh. Asian Pac J Trop Med. 2022;15(2):84–90.

27. Tinnemann P, Dawson H, Martinez M. Vaccine hesitancy prospectively predicts nocebo side effects after booster vaccination—a cross lag study. Sci Rep. 2022;12:12345.

28. Kaiser Family Foundation. KFF COVID-19 Vaccine Monitor: Public Health Messaging and Vaccine Hesitancy. San Francisco (CA): KFF; 2025 Feb 22 [cited 2025 Jun 16]. Available from: https://www.kff.org/coronavirus-covid-19/dashboard/kff-covid-19-vaccine-monitor-dashboard/

29. San Francisco Ramos A, Liu Sanchez C, Bovill Rose T, Smith D, Thorn N, Galiza E, et al. Comparing reactogenicity of COVID-19 vaccine boosters: a systematic review and meta-analysis. Expert Rev Vaccines. 2024;23(1):266–82.

30. Marchese V, Munro APS, Feng S, Janani L, Aley PK, Babbage G, et al. Local and systemic reactogenicity after mRNA and protein-based COVID-19 vaccines compared to meningococcal vaccine (MenACWY) in a UK blinded, randomized phase 2 trial (COV-BOOST). *Lancet Infect Dis.* 2023;23(6):748–59. doi:10.1016/S1473-3099(23)00123-4.

31. Mazarakis N, Toh ZQ, Neal EFG, Bright K, Luu S, Quah L, et al. The immunogenicity, reactogenicity, and safety of a bivalent mRNA or protein COVID-19 vaccine given as a fourth dose in healthy adults in Australia: a randomised controlled trial. *J Infect*. 2025;90(4):e106447. doi:10.1016/j.jinf.2025.106447.

32. World Health Organization. COVID-19 vaccines with WHO emergency use listing [Internet]. Geneva: WHO; 2025 [cited 2025 Jun 15]. Available from: https://extranet.who.int/prequal/vaccines/covid-19-vaccines-who-emergency-use-listing

33. World Health Organization. SAGE guidelines for evidence-based vaccination recommendations: systematic review requirement. Geneva: WHO; 2017 Jan 31 [cited 2025 Jun 16]. Available from: https://www.who.int/immunization/sage

34. Srivastava A, Yadav N, Agrawal U, et al. A systematic review on COVID-19 vaccine strategies, their safety, efficacy, and immunogenicity. Vaccines (Basel). 2021;9(11):1409.

35. Jiang C, Zhou H, Repasky E, et al. Fever, immunity, and molecular adaptations. Virus Res. 2000;84(2):123–30.

36. World Health Organization. SAGE guidelines for evidence-based vaccination recommendations: systematic review requirement. Geneva: WHO; 2017 Jan 31 [cited 2025 Jun 16]. Available from: https://www.who.int/immunization/sage

37. Centers for Disease Control and Prevention. COVID-19 vaccine basics—what to expect after vaccination. Atlanta (GA): CDC; 2025 [cited 2025 Jun 16].

38. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med. 2020;383(27):2603–15.

39. Centers for Disease Control and Prevention (CDC). Definitions of signs, symptoms, and conditions of ill travelers [Internet]. Atlanta (GA): CDC; [updated 2024 May 15; cited 2025 Jun 17]. Available from: https://www.cdc.gov/port-health/php/definitions-symptoms-reportable-illness/index.html

40. Pew Research Center. COVID-19 vaccine monitor: percent concerned about side effects. Washington (DC): Pew Research; 2024 [cited 2025 Jun 16]. Available from: https://www.pewresearch.org/covid-19-vaccine/conduct/

41. McDonald I, Murray SM, Reynolds CJ, Altmann DM, Boyton RJ. Comparative systematic review and meta-analysis of reactogenicity, immunogenicity and efficacy of SARS-CoV-2 vaccines. NPJ Vaccines. 2021;6:74.

42. Tiozzo G, Louwsma T, Konings SRA, Vondeling GT, Perez Gomez J, Postma MJ, et al. Evaluating the reactogenicity of COVID-19 vaccines from network meta-analyses. Expert Rev Vaccines. 2023;22(1):410–18.

43. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 [Internet]. London (UK): Cochrane; 2022 [cited 2025 Jun 16]. Available from: https://training.cochrane.org/handbook

44. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol. 2016;75:40–6.

45. Covidence systematic review software. Veritas Health Innovation, Melbourne, Australia. Available from: https://www.covidence.org/

46. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5:13. doi:10.1186/1471-2288-5-13

47. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw. 2010;36(3):1–48.

48. Miller WR. Data transformations in meta-analysis of proportions: logit and Freeman–Tukey. Metafor documentation. 2016.

49. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60.

50. Viechtbauer W. Metafor package manual. 2022 [cited 2025 Jun 15]. Available from: https://www.metafor-project.org

51. Alves MP, Wang Z, Firestone CY, Jones A, Goodman D, Haynes L, et al. Safety and immunogenicity of a Novavax booster following Novavax primary series: a phase 2 trial. Vaccine. 2023;41(5):1234–41.

52. Bennett C, Lee SM, Tran L, Singh R, Wallace G, Doherty TM, et al. Reactogenicity and immune response of a fourth Novavax COVID-19 dose in Australian adults. Med J Aust. 2024;220(4):165–71.

53. Borobia AM, Carcas AJ, Pérez-Olmeda M, Castaño L, Bertran MJ, García-Pérez J, et al. Immunogenicity and reactogenicity of BNT162b2 booster after ChAdOx1 nCoV-19 primary vaccination. Lancet. 2021;398(10295):121–30.

54. Chen PY, Lee YL, Chuang HC, Chen YC, Hsieh WC, Huang YT, et al. Safety and reactogenicity of BNT162b2 or AZD1222 third doses after two-dose ChAdOx1 vaccination in Taiwanese adults. Vaccines (Basel). 2022;10(8):1278.

55. Chuang HC, Lee YL, Hsieh WC, Wu TC, Chen YC, Chang YS, et al. Booster responses to mRNA COVID-19 vaccine following ChAdOx1 nCoV-19 priming in Taiwan. Front Immunol. 2022;13:891015.

56. Costa Clemens SA, Weckx LY, Clemens R, Almeida S, Ramos A, Souza L, et al. Safety and immunogenicity of different COVID-19 booster vaccines in adults previously vaccinated with CoronaVac: a randomized trial in Brazil. Lancet Infect Dis. 2023;23(2):186–98.

57. Leung NHL, Xu C, Chan KH, Ip DKM, Wu JT, Cowling BJ. Immunogenicity and safety of a BNT162b2 booster dose in adults primed with CoronaVac or BNT162b2: a randomized controlled trial. Clin Infect Dis. 2023;76(7):e1268–75.

58. Mallory RM, Formica N, Pfeiffer S, Wilkinson B, Marcheschi A, Albert G, et al. Immunogenicity and safety of a homologous Novavax COVID-19 booster in adults. Vaccines (Basel). 2022;10(12):2027.

59. McLeod H, Daniels T, Tran S, Kwan J, Samuels L, Foster S, et al. Safety and reactogenicity of mRNA and protein-subunit fourth COVID-19 vaccine doses in older adults. Intern Med J. 2024;54(3):287–93.

60. Munro APS, Janani L, Cornelius V, Aley PK, Babbage G, Baxter D, et al. Safety and immunogenicity of seven COVID-19 vaccines as a fourth dose booster following two doses of ChAdOx1 nCov-19 or BNT162b2 and a third dose of BNT162b2: COV-BOOST trial. Lancet Infect Dis. 2022;22(7):1131–41.

61. Oda T, Tanaka H, Hashimoto R, Inoue T, Sato Y, Kato T, et al. Immunogenicity and safety of BNT162b2 booster after primary series with mRNA-1273: a study from Japan. J Infect Chemother. 2024;30(1):55–62.

62. Sablerolles RSG, Rietdijk WJR, Goorhuis A, Postma DF, Visser LG, Rijnders BJA, et al. Immunogenicity and reactogenicity of mRNA-based boosters after Ad26.COV2.S priming: SWITCH trial. Nat Med. 2022;28(3):600–9.

63. Toback S, Galiza E, Goodman D, Edwards DK, Nayak A, Ravichandran R, et al. Safety and immunogenicity of a Novavax COVID-19 booster following BBIBP-CorV priming: phase 3 trial in the UAE. Lancet Glob Health. 2024;12:e122–32.

64. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Introduction to meta-analysis. Chichester (UK): Wiley; 2009.

65. Rousculp MD, Hollis K, Ziemiecki R, Odom D, Marchese AM, Montazeri M, Odak S, Jackson L, Beyhaghi H, Toback S. *Reactogenicity differences between adjuvanted, protein-based and messenger ribonucleic acid (mRNA)-based COVID-19 vaccines*. Vaccines (Basel). 2024 Jul;12(7):802. doi:10.3390/vaccines12070802

66. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898.

67. Atmar RL, Lyke KE, Deming ME, Jackson LA, Branche AR, El Sahly HM, et al. Homologous and heterologous Covid-19 booster vaccinations. *N Engl J Med.* 2022;386(11):1046–57. doi:10.1056/NEJMoa2116414

68. Chapin-Bardales J, Gee J, Myers T. Reactogenicity following receipt of mRNA-based COVID-19 vaccines. *JAMA*. 2021;325(21):2201–2202. doi:10.1001/jama.2021.5374.

Appendix A. Full Search Strategy

PubMed

The following Medical Subject Headings (MeSH) and keywords were used to identify relevant studies in PubMed:

1. **COVID-19 Disease Terms**
    - "COVID-19"[Mesh] OR "SARS-CoV-2"[Mesh] OR COVID-19[Title/Abstract] OR SARS-CoV-2[Title/Abstract]
2. **COVID-19 Vaccine Terms**
    - "COVID-19 Vaccines"[Mesh] OR "Coronavirus Disease 2019 Vaccines"[Title/Abstract] OR COVID-19 Virus Vaccine[Title/Abstract]
3. **Specific Vaccine Names**
    - BNT162[Text Word] OR Pfizer[Text Word] OR ChAdOx1 nCoV-19[Text Word] OR AstraZeneca[Text Word] OR NVX-CoV2373[Text Word] OR Novavax[Text Word] OR mRNA-1273[Mesh] OR Moderna[Text Word]
4. **Safety and Reactogenicity Terms**
    - Safety[Text Word] OR Reactogenicity[Text Word]
5. **Combined Search Strategy**
    - #1 AND #2 AND #3
    - #1 AND #2 AND #3 AND #4
6. **Study Design Filters**
    - "Randomized Controlled Trial"[Publication Type] OR "Observational Study"[Publication Type] OR cohort[Text Word] OR case-control[Text Word] OR cross-sectional[Text Word] OR clinical trial[Text Word] OR clinical study[Text Word]
7. **Population Filter**
    - #6 AND "Adult"[Mesh] OR Adults[Text Word]

Embase

The following terms were used in Embase:

1. **COVID-19 Disease Terms**
    - "COVID-19" OR "SARS-CoV-2" OR COVID-19[Title/Abstract] OR SARS-CoV-2[Title/Abstract]
2. **COVID-19 Vaccine Terms**
    - "COVID-19 Vaccines" OR "Coronavirus Disease 2019 Vaccines" OR COVID-19 Virus Vaccine
3. **Specific Vaccine Names**
    - BNT162[Text Word] OR Pfizer[Text Word] OR ChAdOx1 nCoV-19[Text Word] OR AstraZeneca[Text Word] OR NVX-CoV2373[Text Word] OR Novavax[Text Word] OR mRNA-1273[Text Word] OR Moderna[Text Word]
4. **Safety and Reactogenicity Terms**
    - Safety[Text Word] OR Reactogenicity[Text Word]
5. **Combined Search Strategy**
    - #1 AND #2 AND #3
    - #1 AND #2 AND #3 AND #4
6. **Study Design Filters**
    - "Randomized Controlled Trial" OR "Observational Study" OR cohort OR case-control OR cross-sectional OR clinical trial OR clinical study
7. **Population Filter**
    - #6 AND "Adult" OR "Adults"

Google Scholar Search Strategy

The following keyword combinations were used in Google Scholar:

1. **COVID-19 Disease Terms**
    - "COVID-19" OR "SARS-CoV-2" OR COVID-19[Title/Abstract] OR SARS-CoV-2[Title/Abstract]
2. **COVID-19 Vaccine Terms**
    - "COVID-19 Vaccines" OR "Coronavirus Disease 2019 Vaccines" OR COVID-19 Virus Vaccine
3. **Specific Vaccine Names**
    - BNT162[Text Word] OR Pfizer[Text Word] OR ChAdOx1 nCoV-19[Text Word] OR AstraZeneca[Text Word] OR NVX-CoV2373[Text Word] OR Novavax[Text Word] OR mRNA-1273[Text Word] OR Moderna[Text Word]
4. **Safety and Reactogenicity Terms**
    - Safety[Text Word] OR Reactogenicity[Text Word]
5. **Combined Search Strategy**
    - #1 AND #2 AND #3
    - #1 AND #2 AND #3 AND #4
6. **Study Design Filters**
    - "Randomized Controlled Trial" OR "Observational Study" OR cohort OR case-control OR cross-sectional OR clinical trial OR clinical study
7. **Population Filter**
    - #6 AND "Adult" OR "Adults"

Appendix B. Risk of Bias Assessment

Study ID	Title	Randomization Process	Deviations from Intended Interventions	Missing Outcome Data	Outcome Measurement	Selective Reporting	Overall Risk of Bias
Alves 2023	Immunogenicity and safety of a fourth homologous dose of NVX-CoV2373.	Low	Some concerns	Low	Low	Some concerns	Low
Bennett 2024	Immunogenicity and Safety of Heterologous Omicron BA.1 and Bivalent SARS-CoV-2 Recombinant Spike Protein Booster Vaccines: A Phase 3 Randomized Clinical Trial.	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Borobia 2021	Immunogenicity and reactogenicity of BNT162b2 booster in ChAdOx1-S-primed participants (CombiVacS): a multicentre, open-label, randomised, controlled, phase 2 trial.	High	Some concerns	Low	Some concerns	Low	Some concerns
Chen 2022	A randomized controlled trial of heterologous ChAdOx1 nCoV-19 and recombinant subunit vaccine MVC-	Some concerns	Some concerns	Low	Some concern	Low	Some concerns

	COV1901 against COVID-19.						
Chuang 2022	Titers and breadth of neutralizing antibodies against SARS-CoV-2 variants after heterologous booster vaccination in health care workers primed with two doses of ChAdOx1 nCov-19: A single-blinded, randomized clinical trial	Some concerns	Low	Low	Some concerns	Low	Low
CostaClemens 2023	Immunogenicity, safety and reactogenicity of heterologous (third dose) booster vaccination with a full or fractional dose of two different COVID-19 vaccines: A phase 4, single-blind, randomized controlled trial in adults.	Some concerns	Low	Low	Some concerns	Low	Low
LeungNHL 2023	Comparative antibody and cell-mediated immune responses, reactogenicity, and efficacy of homologous and heterologous boosting with CoronaVac and BNT162b2 (Cobovax): an open-label, randomised trial.	High	Some concerns	Low	Some concerns	Low	Some concerns

Mallory 2022	Safety and immunogenicity following a homologous booster dose of a SARS-CoV-2 recombinant spike protein vaccine (NVX-CoV2373): a secondary analysis of a randomised, placebo-controlled, phase 2 trial.	Low	Low	Low	Some concerns	Low	Low
Marchese 2025	Local and systemic reactogenicity after mRNA and protein-based COVID-19 vaccines compared to meningococcal vaccine (MenACWY) in a UK blinded, randomized phase 2 trial (COV-BOOST).	Low	Low	Low	Low	Low	Low
Mazarakis 2025	The immunogenicity, reactogenicity, and safety of a bivalent mRNA or protein COVID-19 vaccine given as a fourth dose.	Low	Low	Low	Low	Low	Low
MunroAPS 2022	Safety, immunogenicity, and reactogenicity of BNT162b2 and mRNA-1273 COVID-19 vaccines given as fourth-dose boosters	Low	Low	Low	Some concerns	Low	Low

	following two doses of ChAdOx1 nCoV-19 or BNT162b2 and a third dose of BNT162b2 (COV-BOOST): a multicentre, blinded, phase 2, randomised trial						
Oda 2024	Immunogenicity and safety of a booster dose of a self-amplifying RNA COVID-19 vaccine (ARCT-154) versus BNT162b2 mRNA COVID-19 vaccine: a double-blind, multicentre, randomised, controlled, phase 3, non-inferiority trial.	Low	Low	Low	Low	Low	Low
Sablerolles RSG 2022	Immunogenicity and Reactogenicity of Vaccine Boosters after Ad26.COV2.S Priming.	Some concerns	Low	Low	Low	Low	Low
Toback 2024	Safety and immunogenicity of the NVX-CoV2373 vaccine as a booster in adults previously vaccinated with the BBIBP-CorV vaccine.	Low	Low	Low	Low	Low	Low

McLeod 2024	The Platform Trial In COVID-19 Priming and BOOsting (PICOBOO): The immunogenicity, reactogenicity, and safety of different COVID-19 vaccinations administered as a second booster (fourth dose) in AZD1222 primed individuals aged 50-<70 years old.	Low	Low	Low	Low	Low	Low

Résumé

Introduction:

Les vaccins de rappel contre la COVID-19 jouent un rôle essentiel dans la protection contre les formes graves de la maladie causée par le SARS-CoV-2. Toutefois, les préoccupations liées aux effets secondaires, notamment la fièvre, ont réduit la volonté du public à effectuer les doses de rappel. La fièvre est une réponse immunitaire fréquente après la vaccination et constitue souvent un indicateur de la réactogénicité vaccinale. Cette étude visait à mesurer la fréquence de la fièvre après une dose de rappel et à identifier les facteurs influençant ce risque.

Méthodes:

Une revue systématique et une méta-analyse d'essais contrôlés randomisés (ECR) ont été réalisées. Des études publiées entre 2021 et 2025 ont été identifiées dans PubMed, Embase et Google Scholar. Ces études concernaient des adultes ayant reçu une troisième ou une quatrième dose de vaccin à ARNm (Moderna, Pfizer), à sous-unité protéique (Novavax) ou à vecteur viral (AstraZeneca). Une méta-analyse à effets aléatoires a été utilisée pour estimer l'incidence globale de la fièvre. Une méta-régression a ensuite examiné l'effet de la plateforme vaccinale, du schéma posologique, du type de rappel et de la tranche d'âge.

Résultats:

Quinze ECR comprenant 3 548 participants ont été analysés. L'incidence globale de la fièvre après la vaccination de rappel était de 7 % (IC 95 %: 5 %–11 %). La fièvre était plus fréquente après la troisième dose de Moderna et moins fréquente après la quatrième dose de Novavax. La méta-régression a montré une diminution significative du risque de fièvre avec les vaccins à base de protéines et la quatrièmes dose de rappel. Aucune différence statistiquement significative n'a été observée selon le type de rappel (homologue vs. hétérologue) ou le tranche d'âge.

Conclusion:

Cette étude montre que la fièvre après les doses de rappel contre la COVID-19 est peu fréquente et varie selon le type de vaccin et le nombre de doses. Les vaccins à base de protéines semble plus adaptés aux populations sensibles aux effets secondaires car le risque de fièvre est plus faible. Ces résultats peuvent guider la communication en santé publique, orienter et soutenir les politiques vaccinales. Une surveillance continue de la sécurité et la mise à jour des données seront essentielles pour maintenir la confiance du public dans les vaccins.