Clinical Practice Guidelines on the Management of Emerging and Re-emerging Infectious Diseases in the Philippines

Appendix B. Search Strategies and Appendices of Evidence Summaries

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GUIDELINE QUESTION 1: Should we provide rehabilitative interventions for persons with long coronavirus disease (COVID) symptoms?

Research Question: What is the effect of rehabilitative interventions on clinical signs and symptoms of patients with long COVID?	
Population	Adults (≥18 years) with long COVID, defined by the World Health Organization (WHO) as symptoms at ≥3 months after laboratory confirmed, probable, or suspected COVID-19 infection that persisted for at least two months
Intervention / Treatment	Any non-drug rehabilitative intervention
Comparator	Placebo or sham, usual care, or alternative drug or non-drug interventions
Outcomes	Patient-important outcomes, including fatigue, pain, post-exertional malaise, changes in education or employment status, cognitive function, mental health, dyspnoea, quality of life, patient-reported physical function, recovery or improvement, and serious adverse events
Subgroups (if any)	Not applicable
Methods	Randomized controlled trials (RCTs); observational studies

Evidence Reviewers: Dr. Valentin C. Dones III, Mr. Kerwyn Jim C. Chan, Mr. Howell Henrian G. Bayona
Date of Last Search: January 20, 2025

Statement of the Evidence

Among adults (≥18 years) with long COVID, non-drug rehabilitative interventions are associated with small to moderate improvements in fatigue, dyspnea, cognitive function, physical function, and recovery or overall health status, particularly through modalities such as intermittent aerobic exercise, inspiratory muscle training, and cognitive behavioral therapy. However, the effects of other interventions, including telerehabilitation, photobiomodulation, acupuncture, and transcranial direct current stimulation, remain uncertain due to inconsistent findings and low-quality evidence. Additionally, these interventions are associated with no clear increase in serious adverse events, although the safety data are limited and uncertain due to very low certainty of evidence and very few reported events.

Review Methods

The search strategy focused on identifying rehabilitative interventions for long COVID using structured terms related to population (e.g., long COVID, post-acute sequelae of COVID-19), interventions (e.g., cardiopulmonary rehabilitation, telerehabilitation, cognitive therapy), comparators (e.g., placebo, usual care, no intervention), and methods (systematic reviews (SRs), meta-analyses, randomized controlled trials [RCTs]).

Inclusion criteria required randomized trials enrolling adults (≥18 years) with long COVID, as defined by the World Health Organization (WHO), comparing non-drug interventions against placebo, sham, usual care, or alternative interventions. Post-COVID-19 condition is characterized by symptoms such as fatigue, breathlessness, and cognitive difficulties that persist or emerge around three months after a confirmed or probable SARS-CoV-2

infection, lasting for at least two months without another explanation. These symptoms may continue from the initial illness or appear later, and often fluctuate or recur, impacting daily functioning.[1] No restrictions were placed on date, language, or publication status. Excluded were non-randomized trials, animal studies, acute COVID treatment/prevention trials, and studies focused solely on anosmia/hyposmia.

We used the JBI Critical Appraisal tool for Guideline Development to assess the methodological quality of the living systematic review included in this evidence summary.[2] The evidence summary did not employ meta-analysis but instead used a narrative synthesis approach, presenting unpooled mean differences from individual randomized controlled trials (RCTs). Outcomes such as physical function, fatigue, dyspnea, quality of life, mental health, and recovery were reported separately, along with effect sizes, confidence intervals, and GRADE ratings. Due to substantial heterogeneity in study designs, interventions, populations, and outcome measures, quantitative pooling was deemed inappropriate. Thus, findings were thematically synthesized across intervention domains, including exercise-based, cognitive, device-based, and comprehensive rehabilitation approaches. GRADE methodology was applied to assess the certainty of evidence and to develop recommendations, using structured evidence profiles and summary of findings tables to ensure transparency and consistency in decision-making.[3]

Recommendations from Other Groups

Multiple international guidelines recommend a multidisciplinary and individualized rehabilitation approach for Long COVID, incorporating physical, psychological, and symptom-specific interventions. While most support tailored plans with pacing and hybrid delivery models, the NIH advises supportive care and referrals due to limited evidence for specific therapies.

Group or Agency	Date CPG was released	Recommendation	Strength of Recommendation/Certainty or Quality of Evidence
NICE/SIGN/RCGP (UK) – *Rapid Guideline: Long COVID*(NICE)	25 Jan 2024 (updated)	Advise multidisciplinary rehabilitation encompassing physical, psychological, and psychiatric care with personalized rehabilitation plans including goal-setting, self-management strategies, and pacing of activities.	Expert consensus, recommendations based on limited direct evidence.
WHO(WHO, *Living Guidance for Clinical Management of COVID-19: Rehabilitation of Adults with Post COVID-19 Condition*)	18 Aug 2023	Screen for and manage exertional desaturation or cardiac impairment before initiating physical exercise; recommend multidisciplinary teams, hybrid rehabilitation delivery (in-person and telehealth), and tailored symptom-specific rehab interventions.	Strong recommendation for screening; conditional recommendations for rehabilitation interventions (low to moderate quality evidence).
CDC (USA)(APTA)	21 Jun 2021	Support comprehensive rehabilitation plans individualized to patient's symptoms (physical therapy, occupational therapy, cognitive rehabilitation, etc.) and emphasize psychosocial support.	Expert consensus; evidence evolving.
NIH COVID-19 Treatment Guidelines Panel (USA)(NIH, *Coronavirus Disease 2019 (COVID-19) Treatment Guidelines*)	2021–2023 (living guidelines)	Symptom-based supportive care and referral to appropriate rehabilitation or specialty services; no specific recommended therapies due to insufficient evidence.	No specific treatment recommendation due to insufficient evidence; clinical judgment and supportive care emphasized.
Philippine DOH & PSMID(Tampus et al.)	15 Apr 2021	Individualized pulmonary rehabilitation with breathing exercises, aerobic and strength training, and energy conservation techniques recommended for patients with persistent respiratory symptoms.	Strong recommendation based on moderate-quality evidence.

[1] WHO. *A Clinical Case Definition of Post COVID-19 Condition by a Delphi Consensus, 6 October 2021*. WHO, 23 May 2025, https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1.
[2] Aromataris, E., et al. *JBI Manual for Evidence Synthesis JBI 2024*. 2024, https://doi.org/10.46658/JBIMES-24-01.
[3] Schünemann, Holger, et al. *GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations*. 2013, guidelinedevelopment.org/handbook.

Ongoing Studies and Research Gaps

Ongoing Studies

Several major trials are underway to evaluate rehabilitation for long COVID. In the UK, the STIMULATE-ICP trial (N > 4,500) is assessing an integrated care pathway—including MRI diagnostics and a digital rehab program—versus usual care, with outcomes like fatigue and return-to-work.[4] In the US, the NIH RECOVER initiative has launched eight phase 2 trials testing 13 interventions across symptoms like fatigue, cognitive issues, and sleep disturbances.[5] In Asia, a Hong Kong RCT (NCT04924881) is evaluating a Traditional Chinese Medicine formula for post-COVID fatigue, with results expected in late 2024.

Research Gaps

Despite these active research efforts, important gaps remain in the evidence base for long COVID rehabilitation:

- **Understudied Rehabilitation Modalities:** Key interventions like cognitive rehabilitation, acupuncture, herbal medicine, and pacing strategies for post-exertional malaise show promise but lack large, high-quality RCTs. These approaches are used in practice but remain largely untested in controlled trials.
- **Methodological Limitations:** Many studies have small sample sizes (often 50–60 participants), short follow-up periods (typically under 5 months), and inconsistent outcome measures. High risk of bias due to lack of blinding and varied comparators further limits confidence in results.
- **Gaps in Population Coverage:** Older adults, patients with severe or prolonged long COVID, children, and those in low-resource settings are underrepresented in research. This limits generalizability and highlights the need for studies tailored to vulnerable and underserved populations.
- **Long-Term Outcomes and Sustainability:** Most trials lack long-term follow-up, so it remains unclear whether improvements in fatigue, cognition, or function are sustained. Data on adherence, relapse, and integration into routine care are scarce, as are evaluations of cost-effectiveness and implementation.

Search Strategy

Web of Science

Boolean Operator/s: AND, OR, NOT
Results as of November 7, 2024
** without quotation marks*

Searches	Results	Search Type
1	ALL=(Long COVID)	54,741
2	ALL=(Long COVID-19)	52,326
3	ALL=(Long COVID Syndrome)	9,129
4	ALL=(Long-haul COVID)	229
5	ALL=(“Chronic COVID-19”)	20,029
6	ALL=(Chronic COVID Syndrome)	4,722
7	ALL=("Chronic COVID")	112
8	ALL=(Post-COVID 19)	16,065
9	ALL=(Post-COVID Syndrome)	3,526
10	ALL=(Post-COVID 19 Syndrome)	3,289

[4] Banerjee, A. *A Pragmatic, Multi-Centre, Cluster-Randomised Trial of an Integrated Care Pathway with a Nested, Phase III, Open Label, Adaptive Platform Randomised Drug Trial in Individuals with Long COVID*. NHS Health Research Authority, 10 Jan. 2022, https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/stimulate-icp/#:~:text=We%20will%20recruit%20over%204%2C500,date.
[5] RECOVER. *RECOVER Clinical Trials*. Mar. 2025, https://trials.recovercovid.org/#:~:text=RECOVER%E2%80%99s%208%20clinical%20trials%20are,quality%20of%20life%20the%20most.

Searches	Results	Search Type
11	ALL=(Post-acute COVID-19 syndrome)	1,234
12	ALL=("Chronic SARS-CoV-2")	19
13	ALL=("Chronic SARS-CoV-2 syndrome")	0
14	**Population** #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 ALL=(Long COVID) OR ALL=(Long COVID-19) OR ALL=(Long COVID Syndrome) OR ALL=(Long-haul COVID) OR ALL=("Chronic COVID-19") OR ALL=(Chronic COVID Syndrome) OR ALL=("Chronic COVID") OR ALL=(Post-COVID 19) OR ALL=(Post-COVID Syndrome) OR ALL=(Post-acute COVID-19 syndrome) OR ALL=("Chronic SARS-CoV-2") OR ALL=("Chronic SARS-CoV-2 syndrome")	70,279
15	ALL=(rehabilitati*)	443,077
16	ALL=(Cardiovascular rehabilitation)	27,918
17	ALL=(Pulmonary rehabilitation)	24,710
18	ALL=(Respiratory rehabilitation)	27,049
19	ALL=(Respiratory therapy)	142,526
20	ALL=(Physical Therapy)	323,129
21	ALL=(physiotherap*)	112,930
22	ALL=(exercis*)	820,031
23	ALL=(physical activit*)	797,832
24	ALL=("Physical exercise training")	416
25	ALL=(speech therap*)	30,389
26	ALL=(speech-language therap*)	8,893
27	ALL=(breathing technique*)	13,678
28	ALL=(psychotherap*)	209,125
29	ALL=(nonoperati*)	20,882
30	ALL=(cognitive rehabilitat*)	33,589
31	ALL=(occupational therap*)	52,657
32	ALL=("physical therapy modalities")	1,507
33	ALL=("olfactory training")	345
34	**Intervention** #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 ALL=(rehabilitati*) OR ALL=(Cardiovascular rehabilitation) OR ALL=(Pulmonary rehabilitation) OR ALL=(Respiratory rehabilitation) OR ALL=(Respiratory therapy) OR ALL=(Physical Therapy) OR ALL=(physiotherap*) OR ALL=(exercis*) OR ALL=(physical activit*) OR ALL=("Physical exercise training") OR ALL=(speech therap*) OR ALL=(speech-language therap*) OR ALL=(breathing technique*) OR ALL=(psychotherap*) OR ALL=(nonoperati*) OR ALL=(cognitive rehabilitat*) OR ALL=(occupational therap*) OR ALL=("physical therapy modalities") OR ALL=("olfactory training")	2,473,517
35	ALL=(Placebo)	327,855
36	ALL=("No intervention")	10,808
37	ALL=("standard care")	15,137
38	ALL=(placebo effect)	184,659
39	ALL=("placebo reaction*")	35
40	ALL=("placebo response*")	3,009
41	ALL=("non treatment*")	2,913
42	ALL=("standard treatment")	35,795
43	ALL=("convention* treatment")	16,560
44	**Comparator** #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 ALL=(Placebo) OR ALL=("No intervention") OR ALL=("standard care") OR ALL=(placebo effect) OR ALL=("placebo reaction*") OR ALL=("placebo response*") OR ALL=("non treatment*") OR ALL=("standard treatment") OR ALL=("convention* treatment")	403,484
45	**Population and Intervention and Comparator**	178

Searches	Results	Search Type
	#44 AND #34 AND #14 ALL=(Long COVID) OR ALL=(Long COVID-19) OR ALL=(Long COVID Syndrome) OR ALL=(Long-haul COVID) OR ALL=("Chronic COVID-19") OR ALL=(Chronic COVID Syndrome) OR ALL=("Chronic COVID") OR ALL=(Post-COVID 19) OR ALL=(Post-COVID Syndrome) OR ALL=(Post-acute COVID-19 syndrome) OR ALL=("Chronic SARS-CoV-2") OR ALL=("Chronic SARS-CoV-2 syndrome") **AND** ALL=(rehabilitati*) OR ALL=(Cardiovascular rehabilitation) OR ALL=(Pulmonary rehabilitation) OR ALL=(Respiratory rehabilitation) OR ALL=(Respiratory therapy) OR ALL=(Physical Therapy) OR ALL=(physiotherap*) OR ALL=(exercis*) OR ALL=(physical activit*) OR ALL=("Physical exercise training") OR ALL=(speech therap*) OR ALL=(speech-language therap*) OR ALL=(breathing technique*) OR ALL=(psychotherap*) OR ALL=(nonoperati*) OR ALL=(cognitive rehabilitat*) OR ALL=(occupational therap*) OR ALL=("physical therapy modalities") OR ALL=("olfactory training") **AND** ALL=(Placebo) OR ALL=("No intervention") OR ALL=("standard care") OR ALL=(placebo effect) OR ALL=("placebo reaction*") OR ALL=("placebo response*") OR ALL=("non treatment*") OR ALL=("standard treatment") OR ALL=("convention* treatment")	
46	ALL=(systematic review)	568,881
47	ALL=(meta-analysis)	378,881
48	**Methods** #46 OR #47 ALL=(systematic review) OR ALL=(meta-analysis)	738,469
49	**Population and Intervention and Comparator and Methods** #48 AND #44 AND #34 AND #14 ALL=(Long COVID) OR ALL=(Long COVID-19) OR ALL=(Long COVID Syndrome) OR ALL=(Long-haul COVID) OR ALL=("Chronic COVID-19") OR ALL=(Chronic COVID Syndrome) OR ALL=("Chronic COVID") OR ALL=(Post-COVID 19) OR ALL=(Post-COVID Syndrome) OR ALL=(Post-acute COVID-19 syndrome) OR ALL=("Chronic SARS-CoV-2") OR ALL=("Chronic SARS-CoV-2 syndrome") **AND** ALL=(rehabilitati*) OR ALL=(Cardiovascular rehabilitation) OR ALL=(Pulmonary rehabilitation) OR ALL=(Respiratory rehabilitation) OR ALL=(Respiratory therapy) OR ALL=(Physical Therapy) OR ALL=(physiotherap*) OR ALL=(exercis*) OR ALL=(physical activit*) OR ALL=("Physical exercise training") OR ALL=(speech therap*) OR ALL=(speech-language therap*) OR ALL=(breathing technique*) OR ALL=(psychotherap*) OR ALL=(nonoperati*) OR ALL=(cognitive rehabilitat*) OR ALL=(occupational therap*) OR ALL=("physical therapy modalities") OR ALL=("olfactory training") **AND** ALL=(Placebo) OR ALL=("No intervention") OR ALL=("standard care") OR ALL=(placebo effect) OR ALL=("placebo reaction*") OR ALL=("placebo response*") OR ALL=("non treatment*") OR ALL=("standard treatment") OR ALL=("convention* treatment") **AND** ALL=(systematic review) OR ALL=(meta-analysis)	32

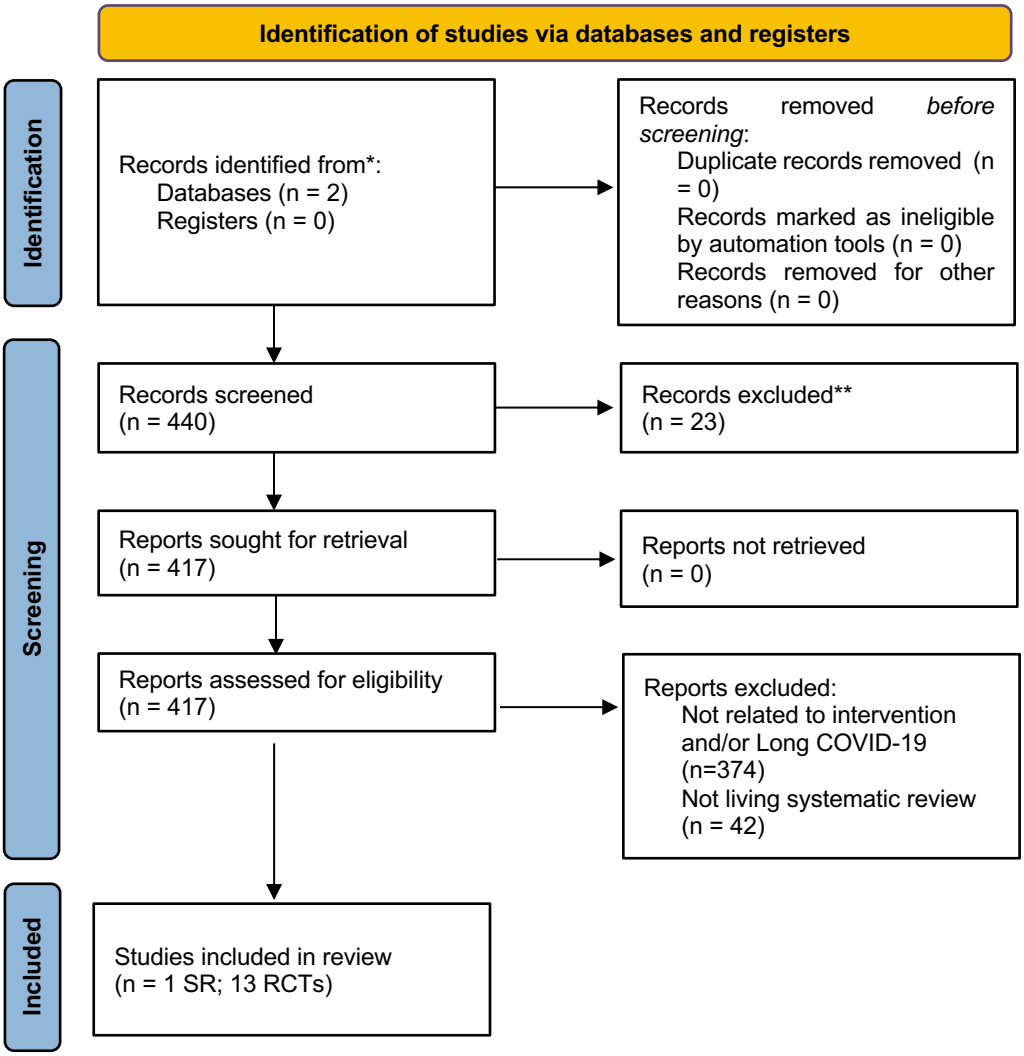
** with quotation marks*

Searches	Results	Search Type
1	ALL=("Long COVID")	6,677
2	ALL=("Long COVID-19")	1,049
3	ALL=("Long COVID Syndrome")	419
4	ALL=("Long-haul COVID")	118
5	ALL=("Chronic COVID-19")	74
6	ALL=("Chronic COVID Syndrome")	18
7	ALL=("Chronic COVID")	112
8	ALL=("Post-COVID 19")	12,676
9	ALL=("Post-COVID Syndrome")	760
10	ALL=("Post-COVID 19 Syndrome")	803
11	ALL=("Post-acute COVID-19 syndrome")	579
12	ALL=("Chronic SARS-CoV-2")	19
13	ALL=("Chronic SARS-CoV-2 syndrome")	0
14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	18,875

Searches	Results	Search Type
	ALL=("Long COVID") OR ALL=("Long COVID-19") OR ALL=("Long COVID Syndrome") OR ALL=("Long-haul COVID") OR ALL=("Chronic COVID-19") OR ALL=("Chronic COVID Syndrome") OR ALL=("Chronic COVID") OR ALL=("Post-COVID 19") OR ALL=("Post-COVID Syndrome") OR ALL=("Post-COVID 19 Syndrome") OR ALL=("Post-acute COVID-19 syndrome") OR ALL=("Chronic SARS-CoV-2") OR ALL=("Chronic SARS-CoV-2 syndrome")	
15	ALL=(rehabilitati*)	443, 077
16	ALL=("Cardiovascular rehabilitation")	560
17	ALL=("Pulmonary rehabilitation")	8,004
18	ALL=("Respiratory rehabilitation")	745
19	ALL=("Physical Therapy")	55,281
20	ALL=(physiotherap*)	112,930
21	ALL=(exercis*)	820,031
22	ALL=(physical activit*)	797,832
23	ALL=("Physical exercise training")	416
24	ALL=(speech therap*)	30,389
25	ALL=(Speech-language therap*)	8,893
26	ALL=(Breathing technique*)	13,678
27	ALL=(psychotherap*)	209,125
28	ALL=(nonoperati*)	20,882
29	ALL=(cognitive rehabilitat*)	33,589
30	ALL=(occupational therap*)	52,657
31	ALL=("Physical Therapy Modalities")	1,507
32	ALL=("Olfactory training")	345
33	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 ALL=(rehabilitati*) OR ALL=("Cardiovascular rehabilitation") OR ALL=("Pulmonary rehabilitation") OR ALL=("Respiratory rehabilitation") OR ALL=("Physical Therapy") OR ALL=(physiotherap*) OR ALL=(exercis*) OR ALL=(physical activit*) OR ALL=("Physical exercise training") OR ALL=(speech therap*) OR ALL=(Speech-language therap*) OR ALL=(Breathing technique*) OR ALL=(psychotherap*) OR ALL=(nonoperati*) OR ALL=(cognitive rehabilitat*) OR ALL=(occupational therap*) OR ALL=("Physical Therapy Modalities") OR ALL=("Olfactory training")	2,184,685
34	ALL=(Placebo)	327,855
35	ALL=("No intervention")	10,808
36	ALL=("Standard Care")	15,137
37	ALL=("Placebo Effect")	4,325
38	ALL=("Placebo reaction*")	35
39	ALL=("placebo response*")	3,009
40	ALL=("non treatment*")	2,913
41	ALL=("Standard treatment")	35,795
42	ALL=("convention* treatment")	16,560
43	#34 OR #36 OR #7 OR #38 OR #39 OR #40 OR #41 OR #42 ALL=(Placebo) OR ALL=("No intervention") OR ALL=("Standard Care") OR ALL=("Placebo Effect") OR ALL=("Placebo reaction*") OR ALL=("placebo response*") OR ALL=("non treatment*") OR ALL=("Standard treatment") OR ALL=("convention* treatment")	394,315
44	#14 AND #33 AND #43 ALL=("Long COVID") OR ALL=("Long COVID-19") OR ALL=("Long COVID Syndrome") OR ALL=("Long-haul COVID") OR ALL=("Chronic COVID-19") OR ALL=("Chronic COVID Syndrome") OR ALL=("Chronic COVID") OR ALL=("Post-COVID 19") OR ALL=("Post-COVID Syndrome") OR ALL=("Post-COVID 19 Syndrome") OR ALL=("Post-acute COVID-19 syndrome") OR ALL=("Chronic SARS-CoV-2") OR ALL=("Chronic SARS-CoV-2 syndrome") **AND** ALL=(rehabilitati*) OR ALL=("Cardiovascular rehabilitation") OR ALL=("Pulmonary rehabilitation") OR ALL=("Respiratory rehabilitation") OR ALL=("Physical Therapy") OR ALL=(physiotherap*) OR ALL=(exercis*) OR ALL=(physical activit*) OR ALL=("Physical exercise training") OR ALL=(speech therap*) OR ALL=(Speech-language therap*) OR ALL=(Breathing technique*) OR ALL=(psychotherap*) OR ALL=(nonoperati*) OR ALL=(cognitive rehabilitat*) OR ALL=(occupational therap*) OR ALL=("Physical Therapy Modalities") OR ALL=("Olfactory training") **AND** ALL=(Placebo) OR ALL=("No intervention") OR	74

Searches	Results	Search Type
	ALL=("Standard Care") OR ALL=("Placebo Effect") OR ALL=("Placebo reaction*") OR ALL=("placebo response*") OR ALL=("non treatment*") OR ALL=("Standard treatment") OR ALL=("convention* treatment")	
45	ALL=(Systematic Review)	568,779
46	ALL=(Meta-analysis)	378,881
47	#45 OR #46 ALL=(Systematic Review) OR ALL=(Meta-analysis)	738,469
48	#44 AND #47 ALL=("Long COVID") OR ALL=("Long COVID-19") OR ALL=("Long COVID Syndrome") OR ALL=("Long-haul COVID") OR ALL=("Chronic COVID-19") OR ALL=("Chronic COVID Syndrome") OR ALL=("Chronic COVID") OR ALL=("Post-COVID 19") OR ALL=("Post-COVID Syndrome") OR ALL=("Post-COVID 19 Syndrome") OR ALL=("Post-acute COVID-19 syndrome") OR ALL=("Chronic SARS-CoV-2") OR ALL=("Chronic SARS-CoV-2 syndrome") **AND** ALL=(rehabilitati*) OR ALL=("Cardiovascular rehabilitation") OR ALL=("Pulmonary rehabilitation") OR ALL=("Respiratory rehabilitation") OR ALL=("Physical Therapy") OR ALL=(physiotherap*) OR ALL=(exercis*) OR ALL=(physical activit*) OR ALL=("Physical exercise training") OR ALL=(speech therap*) OR ALL=(Speech-language therap*) OR ALL=(Breathing technique*) OR ALL=(psychotherap*) OR ALL=(nonoperati*) OR ALL=(cognitive rehabilitat*) OR ALL=(occupational therap*) OR ALL=("Physical Therapy Modalities") OR ALL=("Olfactory training") **AND** ALL=(Placebo) OR ALL=("No intervention") OR ALL=("Standard Care") OR ALL=("Placebo Effect") OR ALL=("Placebo reaction*") OR ALL=("placebo response*") OR ALL=("non treatment*") OR ALL=("Standard treatment") OR ALL=("convention* treatment") **AND** ALL=(Systematic Review) OR ALL=(Meta-analysis)	14
49	#1 OR #8 AND #33 AND #43 ALL=("Long COVID") OR ALL=("Post-COVID 19") **AND** ALL=(rehabilitati*) OR ALL=("Cardiovascular rehabilitation") OR ALL=("Pulmonary rehabilitation") OR ALL=("Respiratory rehabilitation") OR ALL=("Physical Therapy") OR ALL=(physiotherap*) OR ALL=(exercis*) OR ALL=(physical activit*) OR ALL=("Physical exercise training") OR ALL=(speech therap*) OR ALL=(Speech-language therap*) OR ALL=(Breathing technique*) OR ALL=(psychotherap*) OR ALL=(nonoperati*) OR ALL=(cognitive rehabilitat*) OR ALL=(occupational therap*) OR ALL=("Physical Therapy Modalities") OR ALL=("Olfactory training") **AND** ALL=(Placebo) OR ALL=("No intervention") OR ALL=("Standard Care") OR ALL=("Placebo Effect") OR ALL=("Placebo reaction*") OR ALL=("placebo response*") OR ALL=("non treatment*") OR ALL=("Standard treatment") OR ALL=("convention* treatment")	6,696

PRISMA Flow Diagram



Included Studies

Characteristics of Included Studies

Authors	Study Design	Country	Number of participants	Population	Intervention	Comparator	Outcome
Zilberman-Itskovich et al (2022)	RCT	Israel	73	Adults (≥ 18 years old) with persistent post-COVID cognitive symptoms	HBOT, breathing 100% oxygen	Breathing 21% oxygen	Global cognitive function
Toussaint & Bratty (2023)	RCT	United Staes	100	Individuals aged 21-65 with postviral symptoms at least 3 months post-COVID-19 infection	AIR aka The Gupta Program,	Online educational program	Fatigability and energy
Santana et al (2023)	RCT	Not mentioned	70	Patients aged 18-80 with PASC-related fatigue, 3-12 months post-COVID-19	HD-tDCS	Sham HD-tDCS	Fatigability and energy
Mooren et al (2023)	RCT	Germany	110	PCS patients with persistent performance deficits	Continuous aerobic training	Interval aerobic training	Physical exercise capacity and psychological wellbeing
Samper-Pardo et al (2023)	RCT	Spain	100	Long COVID patients (18+) with persistent symptoms, 12+ weeks post-positive COVID-19 test	ReCOVery APP (mobile app for Long COVID rehabilitation)	Treatment as usual	Physical function, cognitive function, and community social support
Romanet et al (2023)	RCT	France	60	Adults with prior COVID-19-related ARDS, post-ICU discharge, with persistent dyspnea	ETR	Standard Physiotherapy	Dyspnea
Mcnarry et al (2022)	RCT	Wales	281	Adults with prior COVID-19 infection and persistent breathlessness	IMT	Usual care waitlist	Health-related quality of life
Mcgregor et al (2024)	RCT	England and Wales	585	Adults discharged from NHS hospitals post-COVID-19 with ongoing physical or mental health issues	REGAIN (online, home-based, supervised group rehabilitation program)	Usual care	Health-related quality of life
Omarova et al (2023)	RCT	Kazakhsan	160	Rehabilitation center patients (18+) with post-COVID-19 condition	CRM and acupuncture	CRM	Bartel index, Borg scale, Modified Dyspnea Scale, and 6-minute walking test performance
Kuut et al (2023)	RCT	Netherlands	114	Adults with post-COVID severe fatigue	CBT	Usual care	Fatigability

Authors	Study Design	Country	Number of participants	Population	Intervention	Comparator	Outcome
Nambi et al (2021)	RCT	Saudi Arabia	76	Men aged 60-80 years with post-COVID-19 sarcopenia	Resistance training combined with either low-intensity or high-intensity aerobic training	High-intensity aerobic training	Muscle strength, muscle mass, kinesiophobia, and quality of life
Elbannaa et al (2022)	RCT	Egypt	100	Obese elderly (60-70) post-COVID patients with fatigue	PBM	Placebo PBM	Functional capacity and fatigability
Ali et al (2023)	RCT	Egypt	60	Stable post-COVID patients (40-50)	Traditional physiotherapy program plus active cycle of breathing technique	Traditional physiotherapy program	Six-minute walk test performance, arterial blood gas parameters, and fatigue levels

Abbreviations: AIR, Amygdala and Insula Retraining; CBT, Cognitive-behavioral therapy; CRM, complex rehabilitation methods; ETR, Exercise Training Rehabilitation; HBOT, hyperbaric oxygen therapy; HD-tDCS, High-Definition transcranial Direct Current Stimulation; IMT, Inspiratory Muscle Training; NHS, National Health Service; PASC, post-acute sequelae of SARS-CoV-2 infection; PBM, Photobiomodulation; PCS, Post-COVID-19 Syndrome; RCT, randomized controlled trial

GUIDELINE QUESTION 2: What clinical manifestations should alert a health practitioner to suspect multisystem inflammatory syndrome in children (MIS-C) with COVID-19?

Research Question: Among children with COVID-19, what clinical and laboratory parameters can accurately identify MIS-C?	
Population	Children diagnosed with COVID-19
Intervention / Treatment	Clinical signs and symptoms; laboratory parameters
Comparator	Not applicable
Outcomes	MIS-C diagnosis
Subgroups (if any)	Children; neonates
Methods	Observational studies; systematic reviews (SRs) of observational studies/diagnostic accuracy studies

Evidence Reviewers: Dr. Sally Jane G. Velasco-Aro, Mr. Howell Henrian G. Bayona
Date of Last Search: January 20, 2025

Statement of the Evidence

Children (MIS-C)

In children with MIS-C, fever (99%), gastrointestinal (70%), cardiovascular (64%), and dermatologic (60%) symptoms were the most common clinical signs. The most frequently elevated inflammatory markers included CRP (86%), D-dimer (81%), ESR (66%), and ferritin (62%). The certainty of evidence is low to moderate.

Neonates (MIS-N)

In neonates with MIS-N, cardiovascular (67%), neurologic (41%), and gastrointestinal symptoms (38%) were most frequently reported. The most elevated laboratory markers included CRP (87%), IL-6 (87%), D-dimer (81%), and BNP (79%).

The overall certainty of evidence is low.

Review Methods

A systematic literature search was up to May 17, 2025 on MEDLINE via PubMed and Embase using a combination of free text terms and medical subject headings (MeSH). We included systematic reviews of observational studies with search dates not later than 3 years prior to this review (May 2022). Individual primary studies involving case series with < 10 patients, expert opinions, and non-English language articles were excluded. The population was limited to children ≤ 18 years of age with an established link to SARS-CoV-2 infection via a positive PCR, antigen test, serology. Rather than assessing all potential clinical and laboratory markers, the analysis was confined to those specified in the current CDC and WHO case definitions for MIS-C. These reference standards were selected due to

their wide use in research and clinical practice, to minimize possible inconsistencies resulting from the use of non-standard diagnostic criteria. Laboratory markers not included in these definitions were excluded from the analysis. Additionally, tests that are not commonly accessible in most healthcare settings in the Philippines, such as auto-antibody tests and cytokine panels, were not considered. Non-specific markers, like ALT/AST levels, were also excluded.

The methodological quality of the systematic reviews was appraised using AMSTAR-2 tool. Pooled data on frequency or prevalence of each clinical feature or select abnormal laboratory findings among MIS-C cases were extracted. For laboratory markers, the mean value was also obtained whenever available. The certainty of evidence for all outcomes were rated using GRADE approach.

Recommendations from Other Groups

In 2022, the American College of Rheumatology has recommended a *tiered approach* towards diagnosis of MIS-C.[6] First, children must present with unremitting fever, an epidemiologic link with SARS-CoV-2 virus, and 2 or more clinical features (see Table below). In patients without life-threatening complications, the recommended laboratory work up is divided into two stages to reduce indiscriminate testing and unnecessary use of resources: Tier 1 involves tests that are easily obtained in most hospitals (e.g., CBC, complete metabolic panel, ESR, SARS-CoV-2 testing); while Tier 2 includes more extensive testing.

Guidance from medical societies in Switzerland also recommend a staged diagnostic approach starting with standard tests for all suspected MIS-C cases followed by more in-depth tests for those with severe disease or diagnostic uncertainty. These recommendations are based on expert opinion and require regular updating due to the evolving nature of MIS-C.

Group/Agency	Recommendation	

2021 Swiss Society of Intensive Care & Pediatric Infectious Diseases Group Switzerland (PIGS)[7]	**Adapted UK Royal College of Pediatrics and Child Health (RCPCH) case definition:**
	
	<u>*Clinical*</u>
	• Age < 18 yo
	• (+) SARS-CoV-2 (by PCR / serology / Ag / COVID exposure within 4 wks)
	• Persistent fever
	• Inflammation (↑ CRP and neutrophils, or lymphopenia)
	• ≥1 organ dysfunction:
	  ○ Gastrointestinal (pain, diarrhea, vomiting, abnormal liver function tests, colitis, ileitis, ascites)
	  ○ Cardiovascular (hypotension, shock, oliguria, myocardial dysfunction, pericardial effusion, coronary artery abnormalities)
	  ○ Respiratory (cough, sore throat, oxygen requirement, patchy infiltrates, pleural effusion)
	  ○ Dermatologic (conjunctivitis, periorbital swelling /redness, mucus membrane changes, rash, lymphadenopathy, swollen hands and feet)
	  ○ Neurologic (headache, confusion, irritability, low consciousness, syncope)
	• Abnormal lab findings indicating inflammation (any combination)
	  ○ Inflammatory markers (↑CRP/fibrinogen/D-dimer/ferritin, hypoalbuminemia, lymphopaenia, neutrophilia)
	  ○ Cardiac biomarkers (↑Troponin T/NT-pro-BNP)
	• Respiratory
	• Exclusion of any other probable cause (e.g., bacterial sepsis, staphylococcal/streptococcal shock syndromes, viral infections)	

	Baseline investigations • Full blood count (FBC)	**Additional investigations in case of suspected MIS-C** • blood gas, lactate, glucose

[6] Henderson LA, Canna SW, Friedman KG, et al. American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 3. Arthritis Rheumatol. 2022;74(4):e1-e20. doi:10.1002/art.42062

[7] Schlapbach LJ, Andre MC, Grazioli S, et al. Best Practice Recommendations for the Diagnosis and Management of Children With Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2 (PIMS-TS; Multisystem Inflammatory Syndrome in Children, MIS-C) in Switzerland. Front Pediatr. 2021;9:667507. Published 2021 May 26. doi:10.3389/fped.2021.667507

<table>
<tr><th>Group/Agency</th><th colspan="2">Recommendation</th></tr>
<tr><td></td><td>• C-reactive protein (CRP)
• Urea, creatinine, electrolytes (U&E)
• Liver function tests (LFTs)
• In addition, as clinically indicated:
  ○ Blood cultures (before antibiotics)
  ○ Urine microscopy and culture
  ○ Lumbar puncture, if no contraindication present
  ○ NPA: respiratory panel, SARS-CoV-2 PCR</td><td>• ESR
• Coagulation: INR, aPTT, Fibrinogen
• D-dimers
• Ferritin
• Albumin
• Troponin T
• NT-pro-BNP
• LDH
• CK, and CK-MB
• SARS-CoV-2 serology
• Store serum (always before IVIG)
• Store EDTA
• 12-lead ECG and echocardiography
• Chest radiograph
• Abdominal ultrasound (if with gastrointestinal symptoms)</td></tr>
<tr><td rowspan="2">2022 American College of Rheumatology Clinical Guidance for MIS-C Version 3</td><td colspan="2">Presence of ALL of the following:
• Unrelenting fever > 38C
• Epidemiologic link with SARS-CoV-2
• At least 2 suggestive clinical features
  ○ Rash
  ○ Gastrointestinal symptoms
  ○ Edema of hands/feet
  ○ Oral mucosal changes
  ○ Conjunctivitis
  ○ Lymphadenopathy
  ○ Neurologic symptoms
• All other causes have been considered

If child does NOT have shock of unclear etiology, start Tier 1 evaluation; otherwise, complete both Tiers 1 and 2.</td></tr>
<tr><td>Tier 1 diagnostic evaluation
• ESR (≥40 mm/hr)
• CRP (≥3mg/dL)

At least 1 suggestive lab feature:
• CBC
• Complete metabolic panel
• PC < 150,000/µl
• ALC < 1,000/µl
• Sodium < 135 mmol/l
• Neutrophilia
• Hypoalbuminemia</td><td>Tier 2 diagnostic evaluation
• BNP
• Troponin T
• Procalcitonin
• Ferritin
• PT
• PTT
• D-dimer
• Fibrinogen
• LDH
• u/a
• Cytokine panel
• Triglycerides
• EKG
• Echocardiogram
• Blood smear</td></tr>
</table>

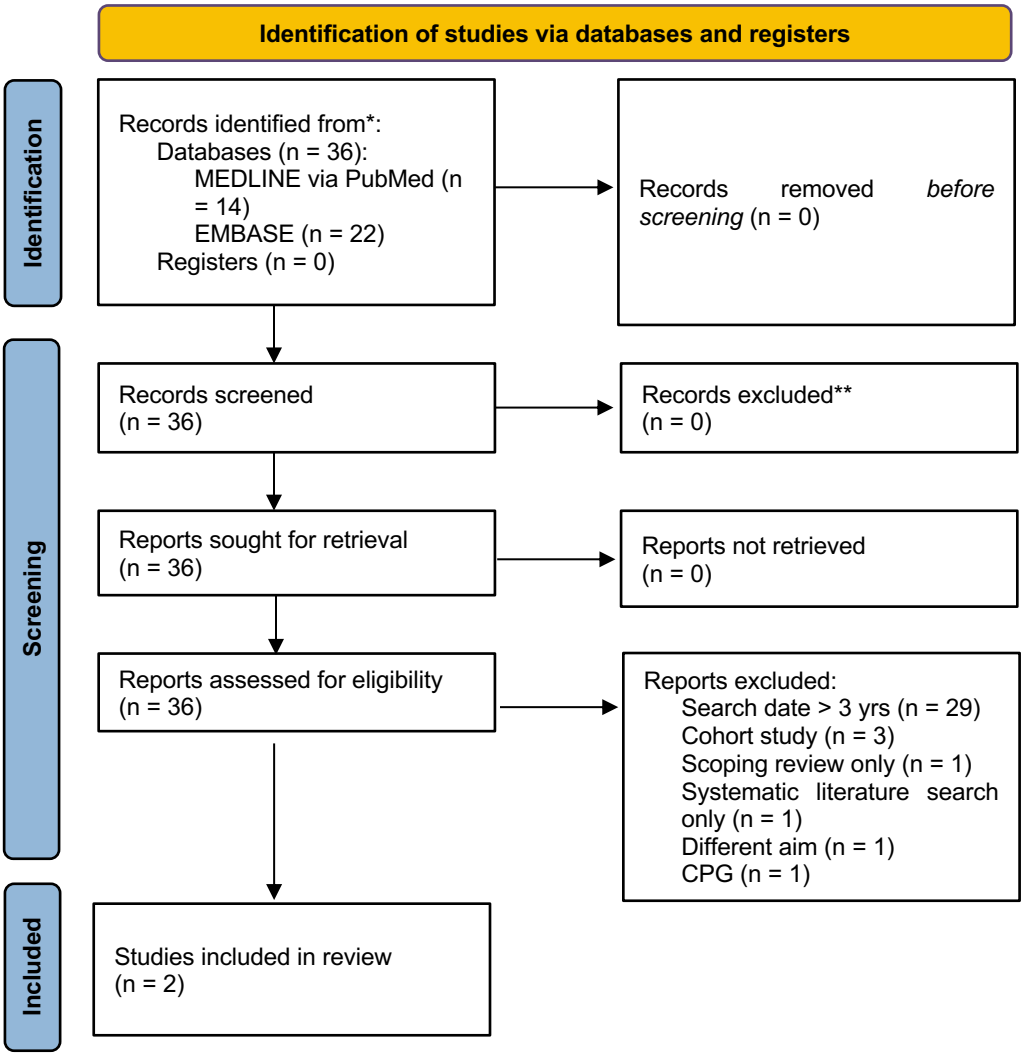
Ongoing Studies and Research Gaps

No local study has been conducted yet describing the clinical presentation of MIS-C cases.

Search Strategy

Database	Search Strategy / Search Terms	Date and Time of Search	Results	
			Yield	Eligible
Medline	(("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s"[All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields]) AND ("covid 19"[All Fields] OR "covid19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[MeSH Terms] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sarscov2"[All Fields] OR "sarscov 2"[All Fields] OR "sars cov2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields] OR "ncov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) AND (("ambulatory care facilities"[MeSH Terms] OR ("ambulatory"[All Fields] AND "care"[All Fields] AND "facilities"[All Fields]) OR "ambulatory care facilities"[All Fields] OR "clinic"[All Fields] OR "clinic s"[All Fields] OR "clinical"[All Fields] OR "clinically"[All Fields] OR "clinicals"[All Fields] OR "clinics"[All Fields]) AND ("diagnosis"[MeSH Subheading] OR "diagnosis"[All Fields] OR "symptoms"[All Fields] OR "diagnosis"[MeSH Terms] OR "symptom"[All Fields] OR "symptom s"[All Fields] OR "symptomes"[All Fields])) AND ("biomarker s"[All Fields] OR "biomarkers"[MeSH Terms] OR "biomarkers"[All Fields] OR "biomarker"[All Fields]) AND (("multisystem"[All Fields] OR "multisystemic"[All Fields] OR "multisystems"[All Fields]) AND ("inflammatories"[All Fields] OR "inflammatory"[All Fields]) AND ("syndrom"[All Fields] OR "syndromal"[All Fields] OR "syndromally"[All Fields] OR "syndrome"[MeSH Terms] OR "syndrome"[All Fields] OR "syndromes"[All Fields] OR "syndrome s"[All Fields] OR "syndromic"[All Fields] OR "syndroms"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s"[All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields]))) AND ((y_5[Filter]) AND (ffrft[Filter]) AND (fha[Filter]) AND (clinicaltrial[Filter] OR meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (fft[Filter]))	April 9, 2025, updated May 17, 2025	19	14
Embase	#13 #12 AND ('meta analysis'/de OR 'meta analysis topic'/de OR 'practice guideline'/de OR 'systematic review'/de) #12 #11 NOT 'nonhuman'/de #11 #6 AND (#7 OR #8) #10 #6 AND #8 #9 #6 AND #7 #8 'odds ratio':ti,ab #7 sensitivity OR specificity OR diagnosis OR accuracy OR 'false positive' OR 'false negative' OR 'detection rate' OR 'receiver operat*':ti,ab,kw #6 #1 OR #2 OR #3 OR #4 OR #5 #5 'mis c':ti,ab #4 'pediatric hyperinflammatory shock':ti,ab #3 'pediatric hyperinflammatory syndrome':ti,ab #2 'pediatric inflammatory multisystem syndrome':ti,ab #1 'pediatric multisystem inflammatory syndrome'/exp OR 'pediatric multisystem inflammatory syndrome'	November 09, 2024, updated May 17, 2025	126	22

PRISMA Flow Diagram



Included Studies

Characteristics of Included Systematic Reviews

Name of systematic review	Aim	Search strategy	Inclusion criteria	No. of studies included
Abbas Q, Ali H, Amjad F, Hussain MZH, Rahman AR, Khan MH, et al. (2024). Clinical presentation, diagnosis and management of multisystem inflammatory syndrome in children (MIS-C): a systematic review. BMJ Paediatr Open, 8(1):e002344. doi: 10.1136/bmjpo-2023-002344.	To investigate and synthesize evolving evidence on its clinical characteristics, management, and outcomes in pediatric patients.	**Databases:** PubMed, CINAHL, Cochrane Library, LitCovid; medRxiv, bioRxiv; with handsearching of references of included studies **Date of last search:** December 2019 to March 2023	**P:** MIS-C (no further specification) **I/C:** MIS-C cases and data related to MIS-C **O:** clinical characteristics, management, outcomes, any effects **M:** Observational studies, excluding case reports (to avoid overrepresentation of extreme cases), review articles, opinions, viewpoints, modeling studies **Other exclusion criteria:** studies with possible duplications of cases (e.g., overlapping time periods)	120 studies 20,881 cases of MIS-C across 5 continents
Mascarenhas D, Goyal M, Haribalakrishna A, Nanavati R, Ish P, Kunal S. Multisystem inflammatory syndrome in neonates (MIS-N): a systematic review. Eur J Pediatr. 2023;182(5):2283-2298. doi:10.1007/s00431-023-04906-4	To systematically review the demographic profile, clinical presentation, laboratory abnormalities, and treatment of MIS-N; describe cases based on their timing of presentation, namely early and late MIS-N	**Databases:** MEDLINE, EMBASE, PubMed, SCOPUS, Google Scholar, Web of Science; bioRxiv, medRxiv; reference list of included studies **Date of last search:** January 1 2020 to Sep 30 2022	**P:** Neonates **E:** MIS-C diagnostic criteria from WHO and CDC modified for neonates: 1. Onset of symptoms from birth to 28 days of life 2. Fever and/or with features suggestive of ≥2 organ system involvement (as fever is relatively uncommon in neonatal period) 3. Laboratory evidence of elevated inflammatory markers (CRP, procalcitonin, ESR, LDH, D-dimer, IL-6, ferritin, fibrinogen) 4. Evidence of SARS-CoV-2 in neonate (+ IgG or IgM antibodies with negative antigen); mother (any history of COVID or positive SARS-CoV-2 antigen or IgM or IgG antibody) 5. No alternative diagnosis given to explain clinical features **O:** demographic features, clinical characteristics, diagnosis/classification of MIS-N, management and outcomes, early and late MIS-N **M:** Observational studies, case reports, case series, brief communications, letters to editors that incorporated details of neonates with MIS-N **Other exclusion criteria:** Studies without full-text version, not in English, no patient data	27 studies (17 case reports, 7 case series, 3 cross-sectional observational) 104 cases of MIS-N

List of Excluded Studies and Reasons for Exclusion

No.	Title of SR	Decision
1	Abrams JY, Godfred-Cato SE, Oster ME, Chow EJ, Koumans EH, et al. (2020). Multisystem Inflammatory Syndrome in Children Associated with SARS-CoV-2: A Systematic Review. J Pediatr, 226:45-54.e1. doi: 10.1016/j.jpeds.2020.08.003. PMID: 32768466.	Exclude – search date > 3 years
2	Ahmed M, Advani S, Moreira A, Zoretic S, Martinez J, et al. (2020). Multisystem inflammatory syndrome in children: A systematic review. EClinicalMedicine, 26:100527. doi: 10.1016/j.eclinm.2020.100527. PMID: 32923992.	Exclude – search date > 3 years
3	Albanji MH, Baghafar AA, Alghanmi YA, Shaaban MM, Alkashlan EA, et al. (2023). Clinical Presentation and Management of Multisystem Inflammatory Syndrome in Children With COVID-19: A Systematic Review. Cureus, 15(10):e46918. doi: 10.7759/cureus.46918. PMID: 37954764.	Exclude – search date > 3 years
4	Baradaran A, Malek A, Moazzen N, Abbasi Shaye Z. (2020). COVID-19 Associated Multisystem Inflammatory Syndrome: A Systematic Review and Meta-analysis. Iran J Allergy Asthma Immunol, 19(6):570-588. doi: 10.18502/ijaai.v19i6.4927. PMID: 33463127.	Exclude – search date > 3 years
5	Baysan, C., Cöl, M., Aydın, S., Gürbüz, S., Özdemir, C., Bekar, T., & Büyükdemirci, E. (2022). Assessment of features of MIS-C and Non-MIS-C patients: Meta-Analysis. Flora the Journal of Infectious Diseases and Clinical Microbiology, 27(1), 158–176. https://doi.org/10.5578/flora.20229912	Exclude – search date > 3 years
6	Buda P, Strauss E, Januszkiewicz-Lewandowska D, et al. Clinical characteristics of children with MIS-C fulfilling classification criteria for macrophage activation syndrome. Front Pediatr. 2022;10:981711. Published 2022 Sep 15. doi:10.3389/fped.2022.981711	Exclude - not a systematic review; cohort study
7	Carmona CA, Kuziez M, Freitas CF, Cyrus JW, Bain J, Karam O. Cardiac manifestations of multisystem inflammatory syndrome of children after SARS-CoV-2 infection: a systematic review and meta-analysis. Cardiol Young. 2023;33(11):2319-2327. doi:10.1017/S104795112300015X	Exclude – search date > 3 years
8	Cowan T, Sio K, Nguyen S. (2021). Inflammatory markers and their prognostic significance in MIS-C: A systematic review and meta-analysis. J Pediatr Infect Dis, 38(4):125-132	Exclude – search date > 3 years
9	Esslami G, Mamishi S, Pourakbari B, Mahmoudi S. Systematic review and meta-analysis on the serological, immunological, and cardiac parameters of the multisystem inflammatory syndrome (MIS-C) associated with SARS-CoV-2 infection. J Med Virol. 2023;95(7):e28927. doi:10.1002/jmv.28927	Exclude – search date > 3 years
10	Farshidgohar M, Oveisi S, Dodangeh S, et al. Evaluation of clinical and laboratory findings in MIS-C patients associated with COVID-19: An experience from the Northwest of Iran. PLoS One. 2024;19(11):e0313843. Published 2024 Nov 21. doi:10.1371/journal.pone.0313843	Exclude - not an SR; cohort study
11	Hoste L, Van Paemel R, Haerynck F. Multisystem inflammatory syndrome in children related to COVID-19: a systematic review. Eur J Pediatr. 2021;180(7):2019-2034. doi:10.1007/s00431-021-03993-5	Exclude – search date > 3 years
12	Henderson LA, Canna SW, Friedman KG, et al. American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 3. Arthritis Rheumatol. 2022;74(4):e1-e20. doi:10.1002/art.42062	Exclude - not an SR; CPG
13	Irfan O, Muttalib F, Tang K, Jiang L, Lassi ZS, Bhutta Z. (2021). Clinical characteristics, treatment and outcomes of paediatric COVID-19: a systematic review and meta-analysis. Arch Dis Child, 106(5):440-448. doi: 10.1136/archdischild-2020-321385. PMID: 33593743	Exclude – search date > 3 years
14	Jiang L, Tang K, Irfan O, Li X, Zhang E, Bhutta Z. (2022). Epidemiology, Clinical Features, and Outcomes of MIS-C and Adolescents – a Live Systematic Review and Meta-analysis. Curr Pediatr Rep, 10(2):19-30. doi: 10.1007/s40124-022-00264-1. PMID: 35540721.	Exclude – search date > 3 years
15	Lee KH, Li H, Lee MH, Park SJ, Kim JS, et al. (2022). Clinical characteristics and treatments of MIS-C: a systematic review. Eur Rev Med Pharmacol Sci, 26(9):3342-3350. doi: 10.26355/eurrev_202205_28754. PMID: 35587087	Exclude – search date > 3 years
16	Lippi G, Mattiuzzi C, Favaloro EJ. Diagnostic value of D-dimer in differentiating multisystem inflammatory syndrome in Children (MIS-C) from Kawasaki disease: systematic literature review and meta-analysis. Diagnosis (Berl). 2024;11(3):231-234. Published 2024 Feb 21. doi:10.1515/dx-2024-0013	Exclude - aims to assess diagnostic accuracy of D-dimer in differentiating MISC from Kawasaki
17	Lo TC, Chen YY. Ocular and Systemic Manifestations in Paediatric Multisystem Inflammatory Syndrome Associated with COVID-19. J Clin Med. 2021;10(13):2953. Published 2021 Jun 30. doi:10.3390/jcm10132953	Exclude - included case series; search date > 3 years
18	Mardi P, Esmaeili M, Iravani P, Abdar ME, Pourrostami K, Qorbani M. (2021). Characteristics of Children With Kawasaki Disease-Like Signs in COVID-19 Pandemic: A Systematic Review. Front Pediatr, 9:625377. doi: 10.3389/fped.2021.625377. PMID: 33816398	Exclude – search date > 3 years

No.	Title of SR	Decision
19	Octavius GS, Tan R, Pratama TA, Budiputri CL, Meliani F, Heriyanto RS, et al. Cardiac manifestations and diagnostic imaging in pediatric inflammatory multisystem syndrome temporally associated with COVID-19: a systematic review. Med J Indones [Internet]. 2022 Mar. 8 [cited 2025 Apr. 25];31(1):20-37. Available from: https://mji.ui.ac.id/journal/index.php/mji/article/view/5754	Exclude – search date > 3 years
20	Panigrahy N, Policarpio J, Ramanathan R. Multisystem inflammatory syndrome in children and SARS-CoV-2: A scoping review [published correction appears in J Pediatr Rehabil Med. 2021;14(1):137. doi: 10.3233/PRM-219001.]. J Pediatr Rehabil Med. 2020;13(3):301-316. doi:10.3233/PRM-200794	Exclude - not a systematic review ; scoping review only
21	Radia T, Williams N, Agrawal P, et al. Multi-system inflammatory syndrome in children & adolescents (MIS-C): A systematic review of clinical features and presentation. Paediatr Respir Rev. 2021;38:51-57. doi:10.1016/j.prrv.2020.08.001	Exclude – search date > 3 years
22	Sachdeva M, Agarwal A, Sra HK, Rana M, Pradhan P, et al. (2022). MIS-C Associated With COVID-19 in Children: A Systematic Review of Studies From India. Indian Pediatr, 59(7):563-569. doi: 10.1007/s13312-022-2559-5. PMID: 35869878.	Exclude – search date > 3 years
23	Samprathi M, Jayashree M. (2021). Biomarkers in COVID-19: An Up-To-Date Review. Front Pediatr, 8:607647. doi: 10.3389/fped.2020.607647. PMID: 33859967	Exclude – search date > 3 years
24	Santos MO, Gonçalves LC, Silva PAN, et al. Multisystem inflammatory syndrome (MIS-C): a systematic review and meta-analysis of clinical characteristics, treatment, and outcomes. J Pediatr (Rio J). 2022;98(4):338-349. doi:10.1016/j.jped.2021.08.006	Exclude – search date > 3 years
25	Shaiba LA, More K, Hadid A, Almaghrabi R, Al Marri M, et al. (2022). Multisystemic Inflammatory Syndrome in Neonates: A Systematic Review. Neonatology, 119(4):405-417. doi: 10.1159/000524202. PMID: 35512651	Exclude – search date > 3 years
26	Shi Q, Wang Z, Liu J, Wang X, Zhou Q, et al. (2021). Risk factors for poor prognosis in children and adolescents with COVID-19: A systematic review and meta-analysis. EClinicalMedicine, 41:101155. doi: 10.1016/j.eclinm.2021.101155. PMID: 34693233.	Exclude – search date > 3 years
27	Shioji N, Aoyama K, Englesakis M, Annich G, Maynes JT. Multisystem inflammatory syndrome in children during the coronavirus disease pandemic of 2019: a review of clinical features and acute phase management. J Anesth. 2021;35(4):563-570. doi:10.1007/s00540-021-02952-6	Exclude - not a systematic review: systematic literature search only
28	Tang Y, Li W, Baskota M, Zhou Q, Fu Z, et al. (2021). MIS-C during the COVID-19 pandemic: a systematic review of published case studies. Transl Pediatr, 10(1):121-135. doi: 10.21037/tp-20-188. PMID: 33633944	Exclude – search date > 3 years
29	Tong T, Yao X, Lin Z, et al. Similarities and differences between MIS-C and KD: a systematic review and meta-analysis. Pediatr Rheumatol Online J. 2022;20(1):112. Published 2022 Dec 5. doi:10.1186/s12969-022-00771-x	Exclude – search date > 3 years
30	Toraih EA, Hussein MH, Elshazli RM, et al. Multisystem inflammatory syndrome in pediatric COVID-19 patients: a meta-analysis. World J Pediatr. 2021;17(2):141-151. doi:10.1007/s12519-021-00419-y	Exclude - did not use WHO/CDC criteria; search date > 3 years
31	Walton M, Raghuveer G, Harahsheh A, et al. Cardiac Biomarkers Aid in Differentiation of Kawasaki Disease from Multisystem Inflammatory Syndrome in Children Associated with COVID-19. Pediatr Cardiol. 2025;46(1):116-126. doi:10.1007/s00246-023-03338-z	Exclude - not a systematic review; observational studuy
32	Williams V, Dash N, Suthar R, Mohandoss V, Jaiswal N, et al. (2020). Clinicolaboratory Profile, Treatment, ICU Needs, and Outcome of Pediatric MIS-C: A Systematic Review. J Pediatr Intensive Care, 11(1):1-12. doi: 10.1055/s-0040-1719173. PMID: 35178272.	Exclude – search date > 3 years
33	Yasuhara J, Watanabe K, Takagi H, Sumitomo N, Kuno T. COVID-19 and multisystem inflammatory syndrome in children: A systematic review and meta-analysis. Pediatr Pulmonol. 2021;56(5):837-848. doi:10.1002/ppul.25245	Exclude – search date > 3 years
34	Zhao Y, Patel J, Huang Y, Yin L, Tang L. (2021). Cardiac markers of MIS-C in COVID-19 patients: A meta-analysis. Am J Emerg Med, 49:62-70. doi: 10.1016/j.ajem.2021.05.044. PMID: 34082189.	Exclude – search date > 3 years
35	Zhao Y, Yin L, Patel J, Tang L, Huang Y. (2021). Inflammatory markers of MIS-C and adolescents associated with COVID-19: A meta-analysis. J Med Virol, 93(7):4358-4369. doi: 10.1002/jmv.26951. PMID: 33739452.	Exclude – search date > 3 years
36	Zhou C, Zhao Y, Wang X, Huang Y, Tang X, Tang L. Laboratory parameters between multisystem inflammatory syndrome in children and Kawasaki disease. Pediatr Pulmonol. 2021;56(12):3688-3698. doi:10.1002/ppul.25687	Exclude – search date > 3 years

Quality Assessment of Included Studies

Assessment of methodological quality of included systematic reviews using AMSTAR-2

Critical domains / items in AMSTAR-2	Mascarenhas 2023	Abbas 2024
Item 2. Protocol registered before commencement of the review	Yes (CRD42022321114)	Yes (CRD42020195823; but no protocol published
Item 4. Adequacy of literature search	Yes	Yes
Item 7. Justification for excluding individual studies	Partial yes	Partial yes
Item 9. Risk of bias from individual studies being included in the review	Yes	Yes
Item 11. Appropriateness of the meta-analytical methods	Yes	Yes
Item 12. Assess potential impact of ROB in primary studies on the meta-analysis results	Yes	Yes
Item 13. Consideration of ROB in primary studies when interpreting the results of the review	Yes	Yes
Item 14. Explanation of heterogeneity in the results	Yes	Yes
Item 15. Assessment of presence and likely impact of publication bias	Partial yes	Yes
Overall confidence in the review results*	**Moderate**	**High**

***High**
No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
Moderate
More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review
Low
One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest
Critically low
More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

Quality assessment of included case series studies in Mascarenhas 2023 (using JBI Critical Appraisal Checklist)

Questions	More 2022	Pawar 2021	Hashiq 2021	Shanker 2021	Shaiba 2021	Balleda 2022	Chaudhuri 2022	Saeedi 2021	Gupta 2022	Tambekar 2022	Dufort 2020
1. Were there clear criteria for inclusion in the case series?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Were valid methods used for identification of the condition for all participants included in the case series?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Did the case series have consecutive inclusion of participants?	No	Yes	No	Yes	Yes	Yes	No	No	No	No	No
5. Did the case series have complete inclusion of participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Was there clear reporting of the demographics of the participants in the study?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No
7. Was there clear reporting of clinical information of the participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Were the outcomes or follow up results of cases clearly reported?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Was statistical analysis appropriate?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Quality assessment of included case reports in Mascarenhas 2023 (using JBI Critical Appraisal Checklist)

Questions	Agarwal 2021	Malek 2022	Divekar 2021	Kappanayil 2021	Shah 2022	Arun 2022	Bakhle 2022	Voddapelli 2022	Amonkar 2021	Schoenmakers 2022	Shinde 2021	Diwakar 2022	Costa 2022	Borkotoky 2021	McCarty 2021	Sojisirikul 2022
1. Were patient's demographic characteristics clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the patient's history clearly described and presented as a timeline?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the current clinical condition of the patient on presentation clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Were diagnostic tests or assessment methods and the results clearly described?	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Was the intervention(s) or treatment procedure(s) clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Was the post-intervention clinical condition clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
7. Were adverse events (harms) or unanticipated events identified and described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Does the case report provide takeaway lessons?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Quality assessment of included studies in Abbas 2024 (using National Heart, Lung, and Blood Institute [NHLBI] quality assessment)

Identifier	Criteria														Score	Mean (Range)
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total (0-9)	
Case Series																7.2 (6-9)
Cattaneo,2021[165]	1	1	1	1	NA	1	1	0	1						7	
Caro-Domínguez,2021[26]	1	1	1	1	NA	1	0	0	1						6	
Pawar,2021[167]	1	1	1	1	1	1	0	0	1						7	
Shahbaznejad,2020[178]	1	1	1	1	1	1	0	0	1						7	
Racko,2021[187]	1	1	1	1	1	1	NR	0	1						7	
Falah,2020[190]	1	1	1	1	1	0	0	0	1						6	
Almoosa,2020[194]	1	1	1	1	1	0	0	0	1						6	
Demir,2021[201]	1	1	1	1	1	1	1	1	1						9	
Türe,2021[202]	1	1	1	1	1	1	NR	1	1						8	
Ramcharan,2020[91]	1	1	1	1	1	1	NR	1	1						8	
Riollano-Cruz,2021[111]	1	1	1	1	1	1	NR	0	1						7	
Young,2021[109]	1	1	1	1	NA	1	1	1	1						8	
Shabab,2021[220]	0	1	1	1	1	1	1	1	1						8	
Case-control																8 (7-9)
Atay,2021[71]	1	1	0	1	1	0	1	0	1	1	NR	NR			7	
Zambrano,2022[225]	1	1	1	1	1	1	1	1	1	0	0	0			9	
Cohort studies																8.8 (5-12)
Bautista-Rodriguez,2021[28]	1	1	1	1	0	1	1	0	1	NA	1	NR	NA	NR	8	
Rosanova,2021[6]	1	1	1	1	0	1	1	0	1	NA	0	NR	NA	1	8	
Yagnam,2021[19]	1	1	1	1	0	1	0	0	1	NA	0	NR	NA	0	6	
Verdugo,2021[20]	1	1	1	1	0	0	0	1	1	NA	1	NR	NA	NR	7	
Mahmoud,2021[163]	1	1	1	1	0	0	0	1	1	NA	1	NR	NA	NR	7	
Rakha,2021[164]	0	1	1	1	0	1	1	0	1	NA	1	NR	NR	NR	7	
Borgel,2021[24]	1	1	1	1	0	0	0	0	1	NA	1	NR	NA	NR	10	
Balagurunathan,2021[35]	1	1	1	1	1	0	0	NA	1	NA	1	NR	NR	0	7	
Sugunan,2021[169]	1	1	1	1	0	0	0	0	1	NA	1	NR	0	NR	6	
Jain,2020[33]	1	1	1	1	0	0	0	0	1	NA	1	NR	NR	NR	6	
Maheshwari,2022[170]	1	1	1	1	0	1	1	1	1	NA	0	NR	0	0	8	
Shobhna Gupta,2021[171]	1	1	1	1	0	0	0	0	1	NA	0	NR	NA	0	5	
Patnaik,2021[172]	1	1	1	1	0	1	1	0	1	NA	0	NR	0	0	7	
Chandran,2021[173]	1	1	1	1	0	0	0	NA	1	NA	1	NR	NA	0	6	

Identifier	Criteria														Score	Mean (Range)
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total (0-9)	
Mamishi,2020[41]	1	1	1	1	0	0	0	1	1	NA	1	NR	NA	0	7	
Ben-Shimol,2021[43]	1	1	1	1	0	1	0	1	1	NA	1	NR	NR	NR	8	
Antúnez-Montes,2021[8]	0	1	1	1	0	0	0	1	1	NA	1	NR	NA	NR	6	
Okarska-Napierała,2020[63]	1	1	1	1	0	0	0	1	1	NA	1	NR	NA	NR	7	
García-Salido,2020[66]	1	1	1	1	0	0	0	1	1	NA	1	NR	NA	NR	7	
Ozsurekci,2021[197]	1	1	1	1	0	0	0	1	1	NA	1	NR	NA	NR	7	
Haslak,2021[75]	1	1	1	1	0	0	0	1	1	NA	1	NR	NA	NR	7	
Alkan,2021[198]	1	1	1	1	0	0	0	1	1	NA	1	NR	NA	NR	7	
Palabiyik,2021[73]	1	1	1	1	0	0	0	0	1	NA	1	NR	NA	NR	6	
Çelikel,2022[199]	1	1	1	1	0	0	0	1	1	NA	1	NR	NA	NR	7	
Tolunay,2021[200]	1	1	1	1	0	0	0	0	1	NA	0	NR	NA	NR	5	
Sen,2022[76]	1	1	1	1	0	0	0	0	1	NA	1	NR	NA	NR	6	
Sa,2021[89]	1	1	1	1	0	0	0	1	1	NA	1	NR	NA	NR	10	
Penner,2021[90]	1	1	1	1	0	1	1	0	1	NA	1	NR	1	NR	9	
Flood,2021[88]	1	1	1	1	0	1	0	1	1	NA	1	NR	NA	NR	8	
Feldstein,2020[212]	1	1	1	1	0	1	1	1	1	NA	1	NR	NA	NR	9	
Jonat,2021[106]	1	1	1	1	0	1	1	1	1	NA	1	NR	1	0	10	
Zhu,2021[213]	1	1	1	1	0	1	0	0	1	NA	1	NR	0	NR	7	
Bowen,2021[215]	1	1	1	1	0	0	0	0	0	NA	1	NR	NA	1	6	
Basalely,2021[107]	1	1	1	1	0	0	1	1	1	NA	1	NR	NA	0	8	
Clouser,2021[216]	1	1	1	1	0	0	1	0	1	NA	1	NR	1	NR	8	
Reiff,2021[104]	1	1	1	1	0	0	0	1	1	NA	1	NR	NA	NR	7	
Sanil,2021[108]	1	1	1	1	1	1	1	NA	1	NA	1	1	1	1	12	
Farooqi,2021[110]	1	1	1	1	0	1	1	0	1	NA	1	1	1	NR	10	
Rodriguez-Smith,2021[217]	1	1	1	1	0	1	0	1	1	NA	1	NR	NA	NR	8	
Lee,2020[218]	1	1	1	0	0	0	1	0	1	NA	1	NR	NA	NR	6	
Feldstein,2021[112]	1	1	1	1	1	1	0	1	1	0	0	0	0	0	8	
Akindele,2021[219]	1	1	1	1	0	1	0	NA	1	NA	1	0	NA	NA	7	
Merckx,2022[16]	1	1	1	1	0	1	1	NA	1	0	1	1	0	0	9	
Abuhammour,2022[188]	1	1	1	1	0	0	1	NA	1	0	1	1	0	0	8	
Hoste,2022[160]	1	1	0	1	0	1	1	NA	1	0	1	1	0	0	8	
Acevedo,2021[161]	1	1	1	1	1	1	1	NA	1	0	1	1	0	1	11	
Homola,2023[162]	1	1	1	1	0	1	1	NA	1	0	1	1	1	0	10	
Hufnagel,2023[166]	1	1	1	1	0	1	1	NA	1	0	1	1	0	0	9	
Mehra,2021[174]	1	1	1	1	1	1	1	NA	1	0	1	1	0	1	11	

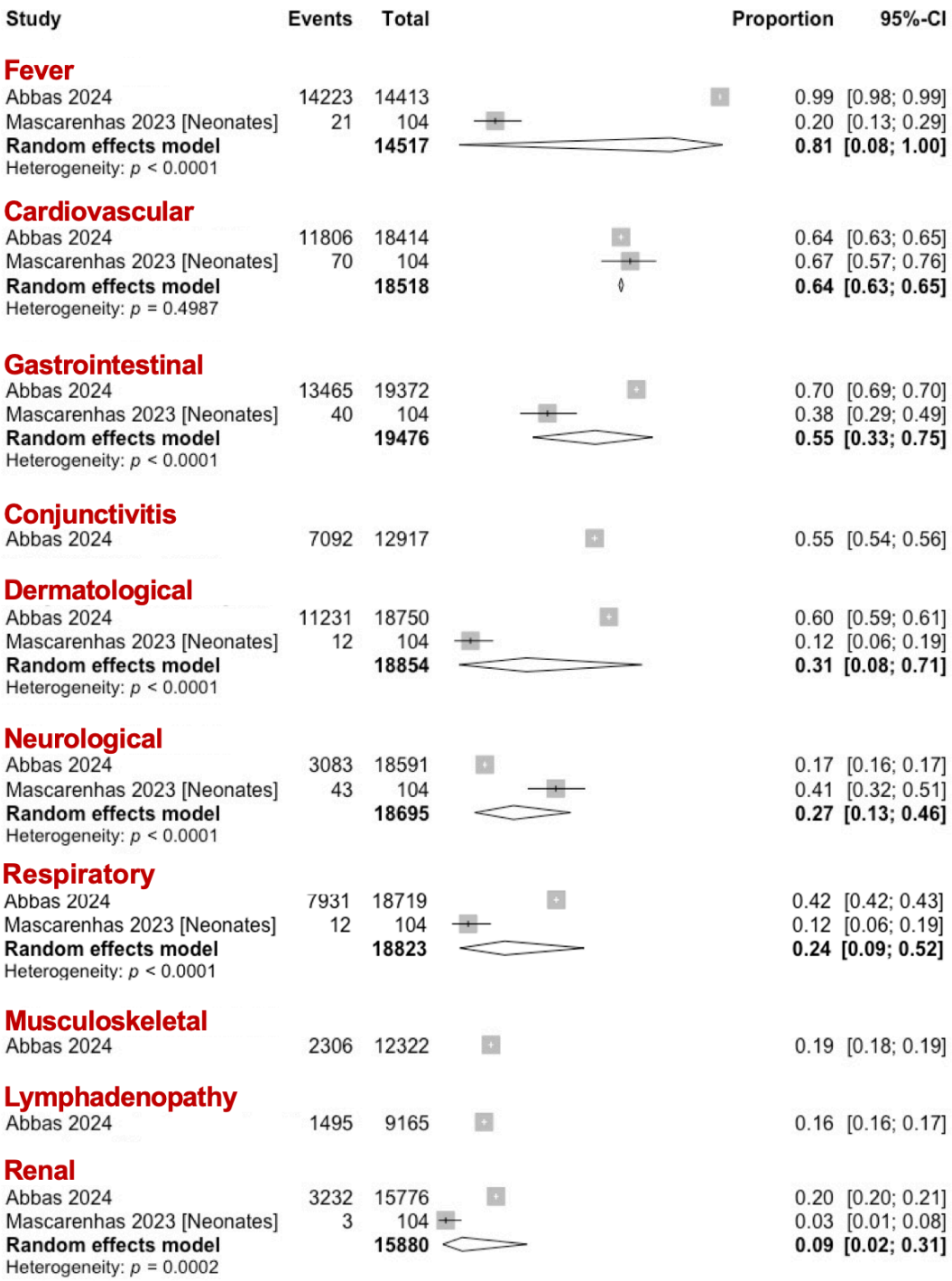
Identifier	Criteria														Score	Mean (Range)
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total (0-9)	
Angurana,2022[34]	1	1	1	1	1	1	1	NA	1	0	1	1	0	0	10	
Dhaliwal,2022[175]	1	1	1	1	1	1	1	NA	1	0	1	1	0	0	10	
Bagri,2022[176]	1	1	1	1	0	1	1	NA	1	0	1	1	0	0	9	
Rostami-Maskopaee,2022[180]	1	1	1	1	1	1	1	NA	1	0	1	1	0	0	10	
Salih,2022[181]	1	1	1	1	1	1	1	NA	1	0	1	1	0	0	10	
Sirico,2022[46]	1	1	1	1	0	1	1	NA	1	0	1	1	0	0	9	
Abbati,2022[183]	1	1	1	1	1	1	1	NA	1	0	1	1	0	0	10	
Camporesi,2022[184]	1	1	0	1	1	1	1	NA	1	0	1	1	0	0	9	
Mannarino,2022[47]	1	1	0	1	0	1	1	NA	1	0	1	1	0	0	8	
Giannattasio,2022[48]	1	1	0	1	1	1	1	NA	1	0	1	1	0	0	9	
Migowa,2022[186]	1	1	1	1	0	1	1	NA	1	0	1	1	0	0	9	
Mohsin,2021[192]	1	1	1	1	1	1	1	NA	1	0	1	1	1	1	12	
Ludwikowska,2021[193]	0	0	1	0	0	1	1	NA	1	0	1	1	0	0	6	
Stasiak,2022[62]	1	1	1	1	1	1	1	NA	1	0	1	1	0	0	10	
Treston,2022[182]	1	1	1	1	1	1	1	NA	1	0	1	1	0	0	10	
Nadua,2022[195]	1	1	1	1	0	1	1	NA	1	0	1	1	0	0	9	
Butters,2022[196]	1	1	1	0	0	1	1	NA	1	0	1	1	0	0	8	
Tagarro,2022[67]	1	1	1	1	1	1	1	NA	1	0	1	1	0	1	11	
Devrim,2022[203]	1	1	1	1	1	1	1	NA	1	0	1	1	0	0	10	
Arslan,2023[204]	1	1	1	1	1	1	1	NA	1	1	1	1	1	0	12	
Yuksel,2022[205]	1	1	1	1	1	1	1	NA	1	0	1	NR	0	0	9	
Erol,2022[206]	1	1	1	1	1	1	1	NA	1	0	1	1	0	0	10	
Tunçer,2022[207]	1	1	1	1	1	1	1	NA	1	0	1	1	1	0	11	
Çiftel,2022[208]	1	1	1	1	1	1	1	NA	1	0	1	1	0	0	10	
Ciftdogan,2022[209]	1	1	1	1	1	1	1	NA	1	0	1	1	1	1	12	
Selçuk,2023[210]	1	1	1	1	1	1	1	NA	1	0	1	1	0	0	10	
Felsenstein,2021[211]	1	1	1	1	1	1	1	NA	1	0	1	1	1	0	11	
Encinosa,2023[221]	1	1	1	1	1	1	1	NA	1	0	1	1	1	1	12	
Evans,2022[222]	1	1	1	1	1	1	1	NA	1	0	1	1	0	0	10	
Khan,2022[223]	1	1	1	1	1	1	1	NA	1	0	1	1	0	0	10	
Das,2023[224]	1	1	1	1	1	1	1	NA	1	0	1	1	1	0	11	
Villacis-Nunez,2022[102]	1	1	1	1	1	1	1	NA	1	0	1	1	1	0	11	
Messiah,2022[226]	1	1	1	1	1	1	1	NA	1	0	1	1	1	1	12	
Fink,2022[189]	1	1	1	1	1	1	1	NA	1	0	1	1	1	1	12	
Sanders,2022[227]	1	1	1	1	1	1	1	NA	1	0	1	1	0	1	11	

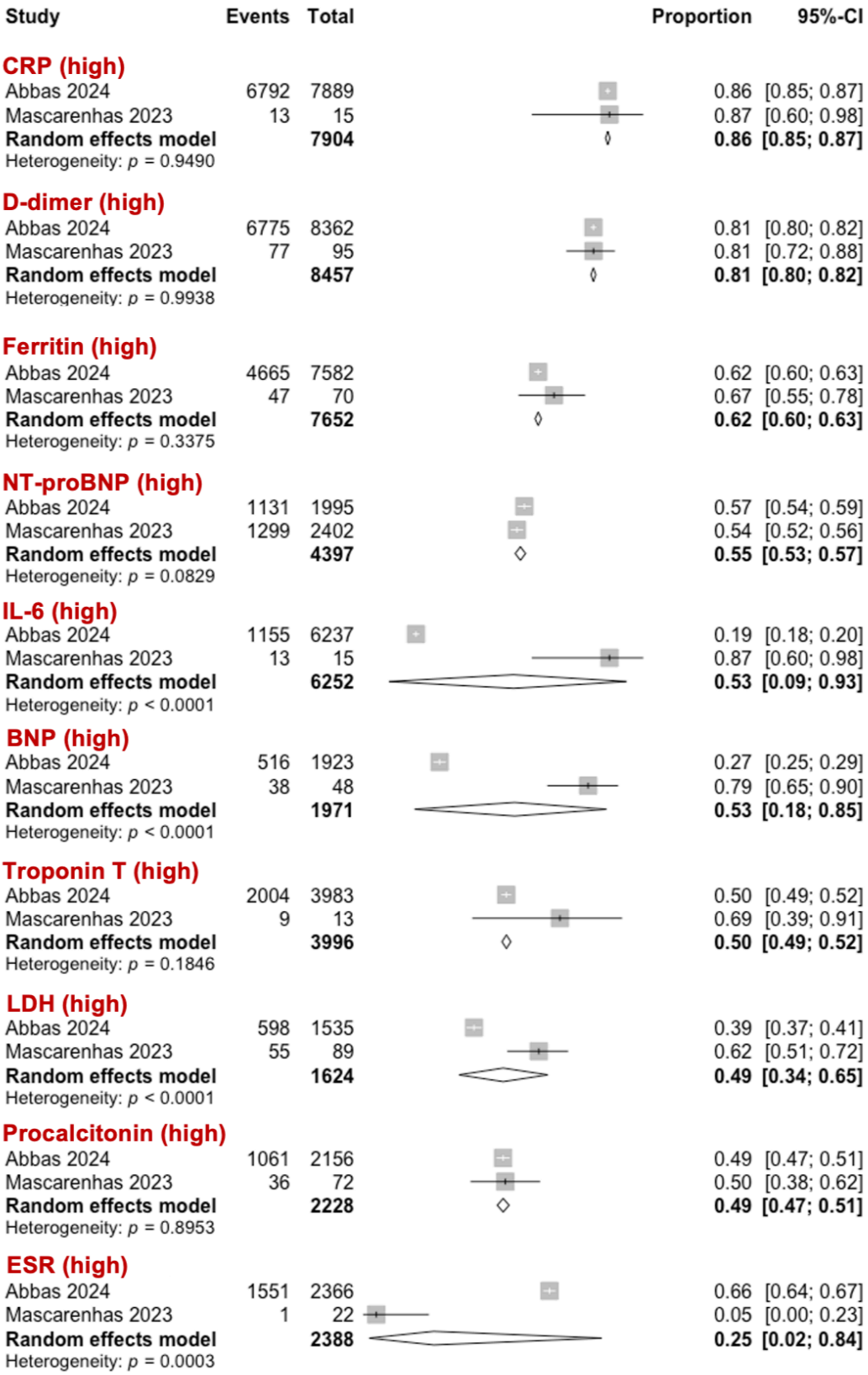
Identifier	Criteria														Score	Mean (Range)
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total (0-9)	
Morparia,2022[228]	1	1	1	1	1	1	1	NA	1	0	1	1	0	0	10	
Son,2022[229]	1	1	1	1	1	1	1	NA	1	0	1	1	0	1	11	
Roberts,2022[105]	1	1	1	1	1	1	1	NA	1	0	1	1	1	0	10	
Martin,2022[230]	1	1	1	1	1	1	1	NA	1	0	1	1	0	1	11	
Harahsheh,2022[113]	1	1	1	1	0	1	1	NA	1	0	1	1	0	0	9	
Miller,2022[231]	1	1	1	1	1	1	1	NA	1	0	1	1	0	0	10	
Chakraborty,2023[232]	1	1	1	1	1	1	1	NA	1	0	1	1	1	0	11	
Phung,2022[233]	1	1	1	1	0	1	1	NA	1	0	0	1	0	0	8	
Cross-sectional studies																7.9 (5-10)
Valverde,2021[27]	1	1	1	1	0	0	0	0	1	NA	1	NR	NA	NR	6	
Belot,2020[23]	1	1	1	1	0	0	0	0	1	NA	0	NR	NA	NR	5	
Sermet-Gaudelus,2021[25]	1	1	1	1	0	0	1	NA	1	NA	1	NR	NA	1	8	
Dhooria,2021[168]	1	1	1	1	1	0	0	NA	1	NA	1	NR	NR	0	7	
Venkataraman,2021[32]	1	1	1	1	0	1	0	1	1	NA	1	1	NA	NR	9	
Bari,2021[191]	1	1	1	1	0	0	0	1	1	NA	1	NR	NA	NR	7	
Başar,2021[74]	1	1	1	1	0	0	1	1	1	NA	1	NR	1	NR	9	
Godfred-Cato,2020[214]	0	1	1	1	0	0	0	0	1	NA	1	NR	NA	NR	8	
Chang,2021[103]	1	1	1	1	0	0	0	0	1	NA	1	NR	NA	1	7	
Relvas-Brandt,2021[9]	0	1	1	1	0	1	1	NA	0	0	1	1	0	0	8	
Putri,2022[177]	1	1	1	1	0	1	1	NA	1	1	1	1	0	0	10	
Sedighi,2022[179]	1	1	0	1	1	1	1	NA	1	0	1	1	0	0	9	
Fabi,2021[185]	1	1	1	1	1	1	1	NA	1	0	1	1	0	0	10	

Abbreviations: NA, not applicable; NR, not reported.

Note: Tables based on Supplementary Material Abbas Q, et al. BMJ Paediatrics Open 2024; 8:e002344. doi: 10.1136/bmjpo-2023-002344

Forest Plots




Study
Events
Total
Proportion
95%-CI
CRP (high)
Abbas 2024 6792 7889 0.86 [0.85; 0.87]
Mascarenhas 2023 13 15 0.87 [0.60; 0.98]
Random effects model 7904 0.86 [0.85; 0.87]
Heterogeneity: p = 0.9490
D-dimer (high)
Abbas 2024 6775 8362 0.81 [0.80; 0.82]
Mascarenhas 2023 77 95 0.81 [0.72; 0.88]
Random effects model 8457 0.81 [0.80; 0.82]
Heterogeneity: p = 0.9938
Ferritin (high)
Abbas 2024 4665 7582 0.62 [0.60; 0.63]
Mascarenhas 2023 47 70 0.67 [0.55; 0.78]
Random effects model 7652 0.62 [0.60; 0.63]
Heterogeneity: p = 0.3375
NT-proBNP (high)
Abbas 2024 1131 1995 0.57 [0.54; 0.59]
Mascarenhas 2023 1299 2402 0.54 [0.52; 0.56]
Random effects model 4397 0.55 [0.53; 0.57]
Heterogeneity: p = 0.0829
IL-6 (high)
Abbas 2024 1155 6237 0.19 [0.18; 0.20]
Mascarenhas 2023 13 15 0.87 [0.60; 0.98]
Random effects model 6252 0.53 [0.09; 0.93]
Heterogeneity: p < 0.0001
BNP (high)
Abbas 2024 516 1923 0.27 [0.25; 0.29]
Mascarenhas 2023 38 48 0.79 [0.65; 0.90]
Random effects model 1971 0.53 [0.18; 0.85]
Heterogeneity: p < 0.0001
Troponin T (high)
Abbas 2024 2004 3983 0.50 [0.49; 0.52]
Mascarenhas 2023 9 13 0.69 [0.39; 0.91]
Random effects model 3996 0.50 [0.49; 0.52]
Heterogeneity: p = 0.1846
LDH (high)
Abbas 2024 598 1535 0.39 [0.37; 0.41]
Mascarenhas 2023 55 89 0.62 [0.51; 0.72]
Random effects model 1624 0.49 [0.34; 0.65]
Heterogeneity: p < 0.0001
Procalcitonin (high)
Abbas 2024 1061 2156 0.49 [0.47; 0.51]
Mascarenhas 2023 36 72 0.50 [0.38; 0.62]
Random effects model 2228 0.49 [0.47; 0.51]
Heterogeneity: p = 0.8953
ESR (high)
Abbas 2024 1551 2366 0.66 [0.64; 0.67]
Mascarenhas 2023 1 22 0.05 [0.00; 0.23]
Random effects model 2388 0.25 [0.02; 0.84]
Heterogeneity: p = 0.0003

GUIDELINE QUESTION 3: Should the 2024-2025 versions of monovalent COVID-19 vaccines be given to adults, adolescents, and children to prevent COVID-19?

Research Question: Among adults, adolescents, and children, should the 2024-2025 versions of monovalent COVID-19 vaccines be given to prevent COVID-19?	
Population	Adults, adolescents, and children
Intervention / Treatment	2024-2025 versions of monovalent COVID-19 vaccines (Pfizer, Moderna, Novavax)
Comparator	Previous versions of COVID-19 vaccines (i.e., bivalent vaccines); no vaccination
Outcomes	Incidence of COVID-19 infection; hospitalization; safety; severe disease; mortality
Subgroups (if any)	Adults; adolescents; children
Methods	RCTs; systematic reviews of RCTs

Evidence Reviewers: Dr. Anton Elepaño, Dr. Katrina Loren R. Reyes, Kerwyn Jim C. Chan, Howell Henrian G. Bayona
Date of Last Search: January 16, 2025

Statement of the Evidence

Among infants, children (6 months to 11yo), adolescents and adults (Age ≥12 yo), updated COVID-19 vaccines are beneficial in terms of reducing medically-attended COVID-19, hospitalization and mortality compared to those who are unvaccinated. Evidence also suggests vaccine effectiveness against hospitalization in elderly and immunocompromised individuals, but the vaccine may offer little or no protection after 4-6 months. The incidence of serious adverse events which include anaphylaxis, and myocarditis/pericarditis is low. The overall certainty of evidence is **very low**.

Review Methods

A systematic search was done until January 11, 2025 using Medline, Scopus, CENTRAL, WHO ICTRP using the search terms Moderna, Spikevax, Pfizer-BioNTech, Comirnaty, Novovax Nuvaxovid, Covovax, COVID-19, 2024-2025, reformulated, updated, monovalent, JN.1 KP.2. Literature search was limited to studies beginning from the discovery of the JN.1 strain in September 2023, which led to the development of monovalent vaccines targeting the spike proteins of both JN.1 and KP.2 (i.e., the 2024-2025 formulation). All types of studies were included and no age restriction set. Subgrouping by population (children, adults, with risk factors (i.e., immunocompromised, elderly) was planned.

Other guidelines which recommended the 2024-2025 COVID-19 vaccines were appraised using the AGREE II. The guidelines were considered acceptable for use if the overall mean score is at least 75% across the six domains and the score for the Rigor of Development domain is at least 75%. Studies were screened by two independent reviewers. Disagreement was settled by a discussion between the two reviewers.

Recommendations from Other Groups

Both the United States Centers for Disease Control (CDC) and Preventions and the Canadian Public Health Agency strongly recommended the use of the 2024-2025 COVID-19 vaccines for the general population despite the low certainty of evidence.

Group or Agency	Recommendation	Guideline Quality (based on AGREE II Overall Score)
US: Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (accessed May 6, 2025)	*Recommendations for general population*[8] ACIP recommends 2024-2025 COVID-19 vaccines as authorized or approved by FDA in persons ≥6 months of age	96%
	Subgroup on elderly and immunocompromised[9] ACIP recommends a second dose of 2024-2025 COVID-19 vaccine for adults ages 65 years and older, a second dose of 2024-2025 COVID-19 vaccine for people ages 6 months-64 years who are moderately or severely immunocompromised, and additional doses (i.e., 3 or more doses) of 2024-2025 COVID-19 vaccine for people ages 6 months and older who are moderately or severely immunocompromised under shared clinical decision-making.	78%
Canada: Public Health Agency National Advisory Committee on Immunization[10] (accessed April 1, 2025)	NACI recommends a COVID-19 vaccine for previously vaccinated and unvaccinated individuals at increased risk of SARS-CoV-2 exposure or severe COVID-19 disease	83%

Ongoing Studies and Research Gaps

NCT06703190 is an ongoing observational trial (retrospective, case-control design) that directly tests the vaccine effectiveness of a 2024-2025 vaccine, specifically the Pfizer-BioNTech BNT162b2 COVID-19 vaccine. The population and outcomes are likewise relevant to the current research question. Patients aged ≥5 years who were symptomatic and tested for SARS-CoV-2 by RAT will be included as cases if they tested positive and as controls if they tested negative, with exposure defined as receipt of the 2024–2025 Pfizer-BioNTech BNT162b2 COVID-19 vaccine ≥14 days before testing, compared to no vaccination or receipt of another 2024–2025 COVID-19 vaccine.[11] The anticipated study completion date is on April 30, 2025 and the trial registration was last updated on April 15, 2025–however, results are still pending.

[8] US Centers for Disease Control and Prevention Advisory Committee on Immunization Practices. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Updated COVID-19 vaccine (2024-2025 Formulation) [Internet]. [cited 2025 Apr 1]. Available from: https://www.cdc.gov/acip/grade/covid-19-2024-2025-6-months-and-older.html

[9] Roper LE. Use of Additional Doses of 2024–2025 COVID-19 Vaccine for Adults Aged≥ 65 Years and Persons Aged≥ 6 Months with Moderate or Severe Immunocompromise: Recommendations of the Advisory Committee on Immunization Practices—United States, 2024. MMWR. Morbidity and Mortality Weekly Report. 2024;73. https://www.cdc.gov/acip/evidence-to-recommendations/covid-19-2024-2025-additional-dose.html

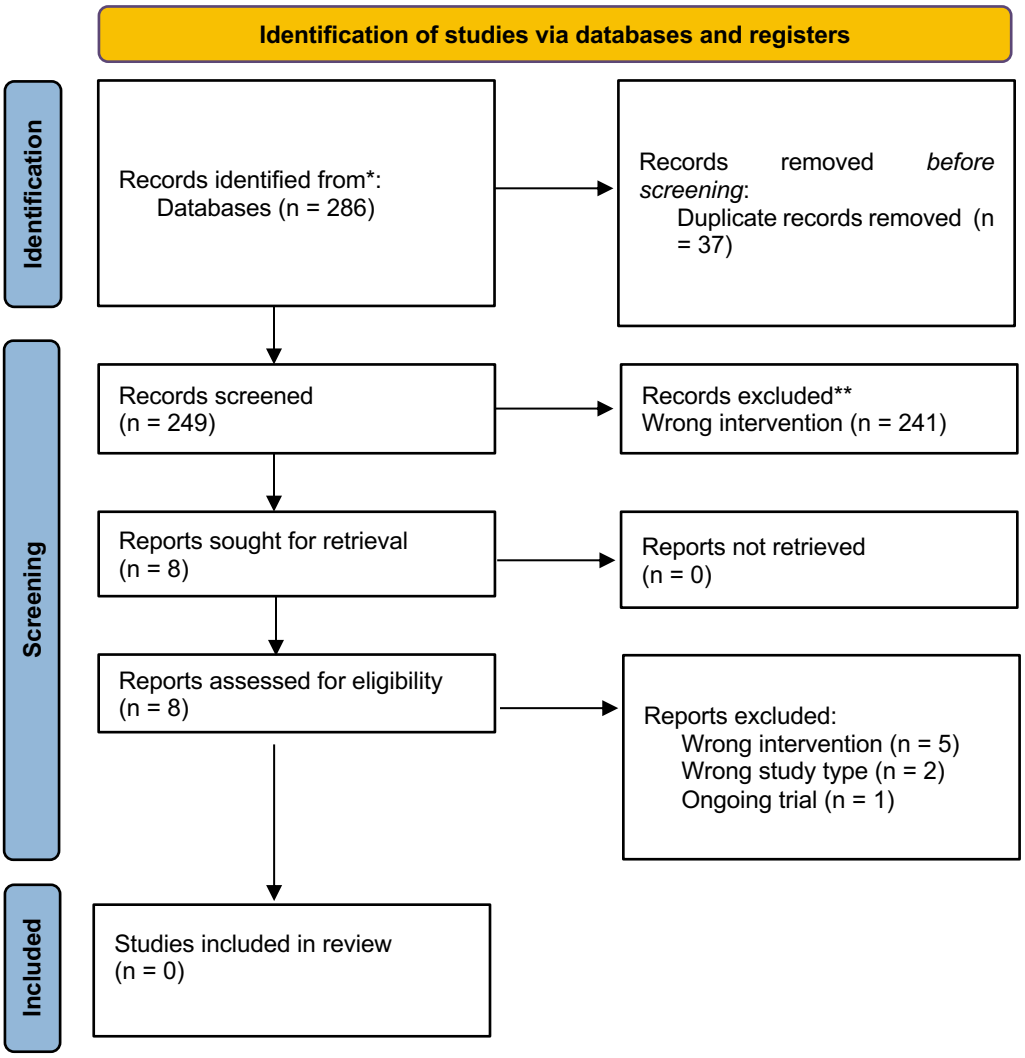
[10] Public Health Agency National Advisory Committee on Immunization. Guidance on the use of COVID-19 vaccines for 2025 to summer 2026 [Internet]. [cited 2025 Apr 1]. Available from: https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/national-advisory-committee-immunization-summary-guidance-covid-19-vaccines-2025-summer-2026.html

[11] ClinicalTrials.gov. Estimated Vaccine Effectiveness and Durability of Pfizer/BioNTech 2024-2025 COVID-19 Vaccine (C4591068) [Internet]. [cited 2025 Apr 1]. Available from: https://clinicaltrials.gov/study/NCT06703190

Search Strategy

Database	Search Strategy / Search Terms	Date and Time of Search	Results	
			Yield	Eligible
Medline	(Moderna OR Spikevax OR Pfizer-BioNTech OR Comirnaty OR Novovax OR Nuvaxovid OR Covovax) AND (COVID-19) AND (2024-2025 OR reformulated OR updated OR monovalent OR JN.1 OR KP.2) Filter: From 2023/9/1	January 13, 2025	1752	0
Scopus	Title, Abstract, Keywords: (Moderna OR Spikevax OR Pfizer-BioNTech OR Comirnaty OR Novovax OR Nuvaxovid OR Covovax) AND (COVID-19) Filter: From 2023/9/1	January 16, 2025	1890	0
CENTRAL	Title, Abstract, Keywords: (Moderna OR Spikevax OR Pfizer-BioNTech OR Comirnaty OR Novovax OR Nuvaxovid OR Covovax) AND (COVID-19) Filter: From 2023/9/1	January 16, 2025	1 review and 63 trials	0
WHO ICTRP	Title, Abstract, Keywords: (Moderna OR Spikevax OR Pfizer-BioNTech OR Comirnaty OR Novovax OR Nuvaxovid OR Covovax) Restrict to COVID-19 Filter: From 2023/9/1	January 13, 2025	29	0
EMBASE	#17 #13 AND (2023:py OR 2024:py) #16 #14 AND (2023:py OR 2024:py) #15 #12 AND (2023:py OR 2024:py OR 2025:py) #14 #12 AND ('phase 2 clinical trial topic'/de OR 'phase 3 clinical trial'/de OR 'phase 3 clinical trial topic'/de OR 'postmarketing surveillance'/de OR 'practice guideline'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial topic'/de) NOT #13 #13 #4 AND #11 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim) #12 #4 AND #11 #11 #5 OR #6 OR #7 OR #8 OR #9 OR #10 #10 spikevax:ti,ab #9 moderna:ti,ab #8 comirnaty:ti,ab #7 'nvx-cov2373 vaccine' #6 nuvaxovid:ti,ab #5 novavax:ti,ab #4 #1 OR #2 OR #3 #3 'covid-19':ti,ab #2 'covid 19':ti,ab #1 'coronavirus disease 2019'/exp OR 'coronavirus disease 2019'	Nov 17, 2024	94	0

PRISMA Flow Diagram



Included Studies

Characteristics of Included Studies

Author Year	Study design	Country	Number of patients	Population	Intervention Group(s)	Control	Outcomes
Estimated Vaccine Effectiveness and Durability of Pfizer/ BioNTech 2024-2025 COVID-19 Vaccine (C4591068) NCT06703190 (ongoing - active, not recruiting) Estimated completion date 04-30-2025	Retrospective observational case-control study	United States	22,692 (estimated enrolment as of 11/22/2024)	Patients ≥5 years of age who tested positive (cases) for negative (controls) to SARS-CoV-2 by RAT at a CVS MinuteClinic and reporting at least one COVID-19 symptom	Receipt of the Pfizer-BioNTech BNT162b2 COVID-19 vaccine (2024-2025 formulation) ≥14 days before testing for SARS-CoV-2	No vaccination or any other 2024-2025 formulated COVID-19 vaccine	Number of Pfizer/BioNTech 2024-2025 formulation vaccinated patients who test positive for SARS-CoV-2 ≥14 days after receipt of vaccine among exposed and unexposed cases and controls

Quality Assessment of Included Studies using AGREE II

AGREE II	USA CDC[1]	USA CDC[2]	Canada	Australia	Ireland	Germany	Spain	South Korea
Domain 1	3/3	3/3	2/3	2/3	2/3	1/3	1/3	1/3
Domain 2	3/3	2/3	2/3	0/3	1/3	0/3	0/3	0/3
Domain 3 (Rigor)	7/8	6/8	6/8	1/8	0/8	1/8	0/8	0/8
Domain 4	3/3	3/3	3/3	3/3	2/3	2/3	0/3	2/3
Domain 5	4/4	3/4	4/4	1/4	1/4	0/4	2/4	2/4
Domain 6	2/2	1/2	2/2	1/2	0/2	1/2	2/2	2/2
Overall assessment	96% (22/23)	78% (18/23)	83% (19/23)	35% (8/23)	26% (6/23)	22% (5/23)	22% (5/23)	30% (7/23)

US: Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (accessed April 1, 2025)
Canada: Public Health Agency National Advisory Committee on Immunization (accessed April 1, 2025)
Australia: Department of Health and Aged Care (accessed January 15, 2025)
Ireland: National Immunisation Advisory Committee (accessed April 1, 2025)
Germany: Ständige Impfkommission am Robert-Koch-Institut (accessed February 20, 2025)
Spain: Public Health Commission (accessed April 1, 2025)
Korea: Korean Society of Infectious Diseases (accessed April 1, 2025)

GUIDELINE QUESTION 4: Should azithromycin, cephalosporin, or amoxicillin be used as alternative post-exposure prophylactic drugs for leptospirosis?

Research Question: Among individuals potentially exposed to leptospira, how effective and safe are azithromycin, cephalosporin, and amoxicillin compared to doxycycline in preventing leptospirosis?	
Population	All patients, any age
Intervention / Treatment	Azithromycin; cephalosporin; amoxicillin
Comparator	Doxycycline
Outcomes	Incidence of leptospirosis infection; safety (any adverse events, serious adverse events)
Subgroups (if any)	Not applicable
Methods	RCTs, non-randomized studies of interventions (NSRIs; includes observational studies)

Evidence Reviewers: Dr. Paul Sherwin O. Tarnate, Mr. Kerwyn Jim C. Chan, Mr. Howell Henrian G. Bayona
Date of Last Search: November 14, 2024; updated May 8, 2025

Statement of the Evidence

Among adults aged 18–65 years, evidence from a single trial suggests that it is very uncertain whether azithromycin reduces or increases the risk of laboratory-confirmed or clinical leptospirosis compared to doxycycline. There is no evidence of using cephalosporins or amoxicillin for post-exposure prophylaxis.

The certainty of evidence is **very low**.

Review Methods

A systematic search was conducted on 12-14 November 2024 using MEDLINE, Cochrane Library, EMBASE, PROSPERO, and HERDIN. The search strategy combined MeSH terms and free-text keywords including "leptospirosis," "*Leptospira*," "infection," "prevention," "exposure," and terms related to chemoprophylaxis, along with specific drug names (penicillin, amoxicillin, cephalosporin, cephalosporin, ceftriaxone, cefotaxime, macrolide, azithromycin, and doxycycline). Only randomized controlled trials (RCTs) comparing azithromycin, any cephalosporin, or penicillin/amoxicillin against doxycycline were included. Outcomes of interest were the incidence of leptospirosis, whether clinically diagnosed or laboratory-confirmed, and the occurrence of serious or non-serious adverse events. No restrictions were placed on participant age, severity of leptospirosis, or the formulation and dosing strategy of the prophylaxis. In the absence of suitable RCTs, observational clinical studies were also considered.

The methodological quality of all included RCTs was appraised using the Risk of Bias 2 (RoB 2) tool for randomized trials. Relevant data consistent with the planned outcomes were extracted and summarized, with these dichotomous outcomes presented as risk ratios (RR) using the Mantel-Haenszel statistical method and accompanied by 95% confidence intervals. Certainty of the evidence was determined based on the risk of bias, indirectness, consistency of the findings, imprecision, and publication bias.

The methodological quality of the systematic reviews was appraised using AMSTAR-2 tool. Pooled data on frequency or prevalence of each clinical feature or select abnormal laboratory findings among MIS-C cases were extracted. For laboratory markers, the mean value was also obtained whenever available. The certainty of evidence for all outcomes were rated using GRADE approach.

Recommendations from Other Groups

The Philippine Department of Health (DOH) follows the national Leptospirosis Clinical Practice Guidelines 2010 for both management and prevention. While alternative treatment options to doxycycline are discussed, there are currently no recommendations for alternative agents to doxycycline for prophylaxis.[12]

Guidelines from the Ministry of Health in Malaysia (2011) recommended azithromycin as an alternative prophylactic regimen—applicable for both pre- and post-exposure—for pregnant women and individuals allergic to doxycycline. These guidelines also acknowledged that the cost-effectiveness and risk-benefit profile of antibiotic prophylaxis for leptospirosis remains unclear and noted that the role of prophylaxis in children has not been studied.

In contrast, the Philippine Pediatric Society - Pediatric Infectious Disease Society of the Philippines, through their 2019 Clinical Practice Guidelines on Leptospirosis, recommended oral penicillin for post-exposure prophylaxis in children, despite the absence of pediatric studies. Although the available evidence is limited, since the only supporting study was conducted in adults, the Stakeholders Panel issued a strong recommendation based on a trend toward benefit for penicillin in preventing symptomatic leptospirosis, even though the results did not reach statistical significance.

Group or Agency	Recommendations for Alternative Prophylaxis	Strength of Recommendation/ Certainty/Quality of Evidence
Ministry of Health Malaysia[13] (2011)	**Pre-exposure prophylaxis:** - Azithromycin 500 mg stat dose then weekly throughout the stay *(for pregnant women and those who are allergic to doxycycline)* **Post-exposure prophylaxis:** - Azithromycin 1 g on day 1 then 500 mg daily for 2 days *(for pregnant women and those who are allergic to doxycycline)* **Notes:** The cost-effectiveness and risk versus benefits of antibiotic prophylaxis for leptospirosis remain unclear. The role of prophylaxis in children has not been adequately studied.	Not indicated
Philippine Pediatric Society – Pediatric Infectious Disease Society of the Philippines[14] (2019)	**Post-exposure prophylaxis:** Oral penicillin may be used for post-exposure prophylaxis in children to prevent symptomatic leptospirosis in high transmission areas but there are no studies in children.	Strong / Very Low

Ongoing Studies and Research Gaps

The current search did not identify any ongoing studies investigating the risk–benefit profile of antibiotic prophylaxis for leptospirosis, nor studies evaluating alternative prophylactic regimens to doxycycline in either

[12] The Leptospirosis Task Force. Leptospirosis CPG 2010. Last accessed: 25 April 2025. Available from: https://www.psmid.org/wp-content/uploads/2020/03/CPG-Leptospirosis-2010.pdf.
[13] Disease Control Division, Department of Public Health, Ministry of Health – Malaysia. Guidelines for the Diagnosis, Management, Prevention, and Control of Leptospirosis in Malaysia. 2011. Last accessed: 12 November 2024. Available from: https://www.moh.gov.my/moh/images/gallery/Garispanduan/GL_Leptospirosis%202011.pdf.
[14] Philippine Pediatric Society – Pediatric Infectious Disease Society of the Philippines. Clinical Practice Guidelines on Leptospirosis in Children. 2019. Last accessed: 12 November 2024. Available from: http://www.pidsphil.org/home/wp-content/uploads/2022/03/CPG-OF-LEPTOSPIROSIS-FINAL-VERSION .pdf.

adult or pediatric populations. This absence of ongoing research highlights a significant gap in the current evidence base.

Several key research gaps were identified during the review. First, there is a pressing need for well-designed randomized controlled trials (RCTs) and non-randomized studies of intervention (NRSIs) that assess alternative regimens, such as azithromycin, cephalosporins, and penicillin/amoxicillin, with doxycycline serving as the control. These studies should incorporate standardized dosing and frequency protocols to facilitate reliable comparisons. Second, evidence in specific high-risk groups, including pregnant women, children, and individuals with contraindications to doxycycline, remains limited and warrants further investigation. Finally, future research should also evaluate the cost-effectiveness and overall risk-benefit balance of prophylactic antibiotic use for leptospirosis, considering regional differences in disease incidence and resource availability.

Search Strategy

Total (duplicates not yet removed): 483 titles

Electronic Databases	Yield	Purpose	Search Strategy
MEDLINE	16	Systematic review and meta-analyses (6) Traditional reviews (4) Clinical trials (5) Quasi-experimental (1)	("leptospirosis"[MeSH Terms] OR "leptospira"[MeSH Terms] OR ("leptospirosis"[MeSH Terms] OR "leptospirosis"[All Fields] OR "leptospiroses"[All Fields]) OR ("leptospira"[MeSH Terms] OR "leptospira"[All Fields] OR "leptospirae"[All Fields] OR "leptospiras"[All Fields]) OR "Leptospira infection"[All Fields] OR "Leptospirosis prevention"[All Fields] OR "Leptospira exposure"[All Fields]) AND (("penicillins"[MeSH Terms] OR ("benzylpenicillins"[All Fields] OR "penicillin g"[MeSH Terms] OR "penicillin g"[All Fields] OR "benzylpenicillin"[All Fields] OR "penicilline"[All Fields] OR "penicillines"[All Fields] OR "penicillins"[MeSH Terms] OR "penicillins"[All Fields] OR "penicillin"[All Fields]) OR "amoxicillin"[MeSH Terms] OR ("amoxicillin"[MeSH Terms] OR "amoxicillin"[All Fields] OR "amoxicilline"[All Fields] OR "amoxicillins"[All Fields]) OR ("cephalosporins"[MeSH Terms] OR ("cephalosporine"[All Fields] OR "cephalosporines"[All Fields] OR "cephalosporins"[MeSH Terms] OR "cephalosporins"[All Fields] OR "cephalosporin"[All Fields]) OR "ceftriaxone"[MeSH Terms] OR ("ceftriaxone"[MeSH Terms] OR "ceftriaxone"[All Fields] OR "ceftriaxon"[All Fields]) OR "cefotaxime"[MeSH Terms] OR ("cefotaxime"[MeSH Terms] OR "cefotaxime"[All Fields] OR "cefotaxim"[All Fields])) OR ("macrolides"[MeSH Terms] OR ("macrolid"[All Fields] OR "macrolides"[MeSH Terms] OR "macrolides"[All Fields] OR "macrolide"[All Fields] OR "macrolids"[All Fields]) OR "azithromycin"[MeSH Terms] OR ("azithromycin"[MeSH Terms] OR "azithromycin"[All Fields] OR "azithromycine"[All Fields] OR "azithromycin s"[All Fields])) OR ("doxycycline"[MeSH Terms] OR ("doxycycline"[MeSH Terms] OR "doxycycline"[All Fields] OR "doxycyclin"[All Fields]))) AND ("post exposure prophylaxis"[MeSH Terms] OR "antibiotic prophylaxis"[MeSH Terms] OR "chemoprevention"[MeSH Terms] OR "PEP"[All Fields] OR ("antibiotic prophylaxis"[MeSH Terms] OR ("antibiotic"[All Fields] AND "prophylaxis"[All Fields]) OR "antibiotic prophylaxis"[All Fields]) OR ("chemoprevention"[MeSH Terms] OR "chemoprevention"[All Fields] OR "chemoprophylaxis"[All Fields] OR "chemoprophylaxy"[All Fields]) OR (("condoms"[MeSH Terms] OR "condoms"[All Fields] OR "prophylactic"[All Fields] OR "prophylactically"[All Fields] OR "prophylactics"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "treatments"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "treatments"[All Fields])) OR ("post exposure prophylaxis"[MeSH Terms] OR ("post exposure"[All Fields] AND "prophylaxis"[All Fields]) OR "post exposure prophylaxis"[All Fields] OR ("post"[All Fields] AND "exposure"[All Fields] AND "prophylaxis"[All Fields]) OR "post exposure prophylaxis"[All Fields]))) *Filter:* Systematic reviews, meta-analysis, traditional reviews, clinical trials, quasi-experimental studies

Electronic Databases	Yield	Purpose	Search Strategy
CENTRAL	15	Cochrane reviews (7) Clinical trials (8)	[(MeSH descriptor: [Leptospirosis] explode all trees) OR (leptospirosis) OR (leptospira) OR (leptospira infection) OR (leptospirosis prevention) OR (leptospirosis exposure)] AND [(MeSH descriptor: [Post-Exposure Prophylaxis] explode all trees) OR (antibiotic prophylaxis) OR (chemoprophylaxis) OR (prophylactic treatment)]
EMBASE	469	Systematic reviews and meta-analyses (60) Clinical trials (26) Observational studies (383)	[('leptospira interrogans':ab,ti) OR ('leptospira':ab,ti) OR ('leptospirosis'/exp OR 'leptospirosis' OR 'leptospirosis':ab,ti)] AND [('antibiotic prophylaxis') OR ('prophylaxis':ab,ti) OR (prophyla*:ab,ti OR prevent*:ab,ti OR protec*:ab,ti OR premedic*:ab,ti OR chemoprophyla*:ab,ti)] Filter [SR/MA]: ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim) Filter [CT]: ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) Filter [Obs]: ('case control study'/de OR 'case report'/de OR 'clinical trial'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'cross sectional study'/de OR 'longitudinal study'/de OR 'observational study'/de OR 'prospective study'/de OR 'retrospective study'/de) NOT 'nonhuman'/de
PROSPERO (via crd.york.ac.uk)	13	Systematic reviews and meta-analyses (13)	MeSH DESCRIPTOR leptospirosis EXPLODE ALL TREES
HERDIN (herdin.ph)	2	Local studies - Interim statement (1) - Proceedings (1)	Leptospirosis AND prophylaxis

Relevant Clinical Practice Guideline Search

Philippine Society of Microbiology and Infectious Diseases. Leptospirosis Clinical Practice Guidelines. 2010. Last accessed: 12 November 2023.

- Recommended doxycycline as prophylaxis for leptospirosis, but did not provide chemoprophylactic alternatives

Disease Control Division, Department of Public Health, Ministry of Health – Malaysia. Guidelines for the Diagnosis, Management, Prevention, and Control of Leptospirosis in Malaysia. 2011. Last accessed: 12 November 2023.

- Recommended doxycycline and azithromycin (as alternative) for leptospirosis chemoprophylaxis but no comparisons in terms of outcomes were made

National Centre for Disease Control – India. National Guidelines: Diagnosis, Case Management, Prevention and Control of Leptospirosis. 2015. Last accessed: 12 November 2023.

- Recommended doxycycline as prophylaxis for leptospirosis, but did not provide chemoprophylactic alternatives

Philippine Pediatric Society – Pediatric Infectious Disease Society of the Philippines. Clinical Practice Guidelines on Leptospirosis in Children. 2019. Last accessed: 12 November 2023.

- Recommended doxycycline as post-exposure prophylaxis in preventing leptospirosis in children
- Recommended oral penicillin as an alternative but acknowledges absence of studies in children

Detailed Search: MEDLINE

Date of Search: 12 November 2024; Updated: 07 May 2025

No.	Query	Filters	Search Details	Results	Time
14	#10 OR #11 OR #12 OR #13 (S*tudies for screening*)			16	20:56:54
13	#9 AND #14	Non-randomized trials or quasi-experimental study types	#9 AND ("Controlled Before-After Studies"[Mesh:NoExp] OR "Interrupted Time Series Analysis"[Mesh:NoExp] OR (("before after"[TIAB:~2] AND intervention[TIAB])) OR "interrupted time"[TIAB] OR "non randomised"[TIAB:~1] OR "non randomized"[TIAB:~1] OR nonequivalent[TIAB] OR nonrandomised[TIAB] OR nonrandomized[TIAB] OR ("one group"[TIAB] AND ("post test"[TIAB] OR "pre test"[TIAB] OR pretest[TIAB] OR posttest[TIAB])) OR ((pretest[TIAB] OR ("pre intervention"[TIAB:~4] OR "pre posttest"[TIAB:~4] OR "pre test"[TIAB:~4])) AND (posttest[TIAB] OR "post intervention"[TIAB:~4] OR "post test"[TIAB:~4])) OR "pretest posttest"[TIAB:~4] OR quasiexperimental[TIAB] OR "quasi experimental"[TIAB:~1] OR ("single group"[TIAB:~1] AND "group study"[TIAB:~1]) OR "uncontrolled studies"[TIAB:~1] OR "uncontrolled study"[TIAB:~1])	1	20:52:16
12	#9 AND #13	Clinical trials	#9 AND (("Adaptive Clinical Trial" [PTYP:NoExp] OR "Clinical Trial" [PTYP:NoExp] OR "clinical trial, phase i"[PTYP] OR "clinical trial, phase ii"[PTYP] OR "clinical trial, phase iii"[PTYP] OR "clinical trial, phase iv"[PTYP] OR "controlled clinical trial"[PTYP] OR "Equivalence Trial"[PTYP] OR "multicenter study"[PTYP] OR "pragmatic clinical trial"[PTYP] OR "randomized controlled trial"[PTYP] OR "adaptive clinical trials as topic"[MeSH:noexp] OR "Clinical Studies as Topic"[mesh:noexp] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH:noexp] OR "clinical trials, phase ii as topic"[MeSH:noexp] OR "clinical trials, phase iii as topic"[MeSH:noexp] OR "clinical trials, phase iv as topic"[MeSH:noexp] OR "controlled clinical trials as topic"[MeSH:noexp] OR "Double-Blind Method"[Mesh] OR "early termination of clinical trials"[MeSH:noexp] OR "Equivalence Trials as Topic"[MeSH:noexp] OR "Intention to Treat Analysis"[MeSH:noexp] OR "multicenter studies as topic"[MeSH:noexp] OR "Non-Randomized Controlled Trials as Topic"[MeSH:noexp] OR "Pragmatic Clinical Trials as Topic"[MeSH:noexp] OR "randomized controlled trials as topic"[MeSH:noexp] OR "2 arm"[TIAB] OR "two arm"[TIAB] OR "3 arm"[TIAB] OR "three arm"[TIAB] OR "4 arm"[TIAB] OR "four arm"[TIAB] OR "clinical studies"[TIAB:~3] OR "clinical study"[TIAB:~3] OR "clinical trial"[TIAB:~3] OR "clinical trials"[TIAB:~3] OR "controlled studies"[TIAB:~3] OR "controlled	12	20:48:46

No.	Query	Filters	Search Details	Results	Time
			study"[TIAB:~3] OR "controlled trial"[TIAB:~3] OR "controlled trials"[TIAB:~3] OR ("cross-over"[TIAB] AND "over trial"[TIAB:~3]) OR ("cross-over"[TIAB] AND "over trials"[TIAB:~3]) OR "crossover trial"[TIAB:~3] OR "crossover trials"[TIAB:~3] OR "equivalent study"[TIAB:~3] OR "equivalent trial"[TIAB:~3] OR "equivalent trials"[TIAB:~3] OR intervention[TI] OR "pragmatic study"[TIAB:~3] OR "pragmatic trial"[TIAB:~3] OR "pragmatic trials"[TIAB:~3] OR "randomised cross"[TIAB] OR "randomised crossover"[TIAB] OR "randomized cross"[TIAB:~3] OR "randomized crossover"[TIAB:~3] OR "randomised studies"[TIAB:~3] OR "randomised study"[TIAB:~3] OR "randomised trial"[TIAB:~3] OR "randomised trials"[TIAB:~3] OR "randomized studies"[TIAB:~3] OR "randomized study"[TIAB:~3] OR "randomized trial"[TIAB:~3] OR "randomized trials"[TIAB:~3] OR "stepped wedge"[TIAB] OR ("window opportunity"[tiab:~1] AND trial[tiab]) OR "phase I"[TIAB] OR "phase II"[TIAB] OR "phase III"[TIAB] OR "phase IV"[TIAB] OR "phase 1"[TIAB] OR "phase 2"[TIAB] OR "phase 3"[TIAB] OR "phase 4"[TIAB] OR "single blind"[TIAB] OR "single blinded"[TIAB] OR "single mask"[TIAB] OR "single masked"[TIAB] OR "double blind"[TIAB] OR "double blinded"[TIAB] OR "double mask"[TIAB] OR "double masked"[TIAB] OR "triple blind"[TIAB] OR "triple blinded"[TIAB] OR "triple masked"[TIAB] OR "tripled blinded"[TIAB]))		
11	#9 AND #11	Traditional literature (non-systematic) reviews	#9 AND ((review[pt] OR "Integrated review"[TIAB] OR "integrated reviews"[TIAB] OR "integrative review"[TIAB:~1] OR "integrative reviews"[TIAB:~1] OR "narrative review"[TIAB:~1] OR "narrative reviews"[TIAB:~1] OR overview[tiab] OR ("state art "[TIAB:~2] AND ("art research"[TIAB:~1] OR "art review"[TIAB:~1])) OR ("state science"[TIAB:~3] AND ("science research"[TIAB:~2] OR "science review"[TIAB:~2]))) NOT (systematic[ti] OR scoping[TI]))	9	20:46:11
10	#9 AND #10	Systematic reviews, Meta-analysis	#9 AND (("Systematic Review"[Publication Type:NoExp] OR "Systematic Reviews as Topic"[mesh:noexp] OR "Cochrane Database Syst Rev"[Journal] OR "Evid Rep Technol Assess (Full Rep)"[jour] OR "Evid Rep Technol Assess (Summ)"[jour] OR "scoping"[TI] OR "systematic"[TI] OR ((("comprehensive analysis" [TIAB:~1] OR "comprehensive review" [TIAB:~1] OR "comprehensively reviewed" [TIAB:~1] OR "literature search" [TIAB:~1] OR "literature searches" [TIAB:~1] OR "scoping search" [TIAB:~1] OR "scoping searches" [TIAB:~1]) NOT "narrative review"[TI]) OR "pooled study" [TIAB:~1] OR "systematic search" [TIAB:~1] OR "systematic searches"	6	20:42:58

No.	Query	Filters	Search Details	Results	Time
			[TIAB:~1] OR "systematically searched" [TIAB:~1) AND (databases[TIAB] OR "cinahl" [TIAB] OR "cochrane" [TIAB] OR "embase" [TIAB] OR "psycinfo" [TIAB] OR "pubmed" [TIAB] OR "medline" [TIAB] OR "scopus" [TIAB] OR "web science" [TIAB:~1] OR "bibliographic review" [TIAB:~1] OR "bibliographic reviews" [TIAB:~1] OR "literature review" [TIAB:~1] OR "literature reviews" [TIAB:~1]) OR (("electronic database" [TIAB:~1] OR "electronic databases" [TIAB:~1] OR "databases searched" [TIAB:~3]) AND (eligibility [TIAB] OR excluded [TIAB] OR exclusion [TIAB] OR included [TIAB] OR inclusion [TIAB])) OR ("comparative effectiveness" [TIAB:~1] AND "effectiveness review" [TIAB:~2]) OR ("critical interpretive" [TIAB:~1] AND ("interpretive review" [TIAB:~0] OR "interpretive synthesis" [TIAB:~0])) OR ("diagnostic test" [TIAB:~0] AND ("accuracy review" [TIAB] OR "accuracy reviews" [TIAB] OR "accuracy studies" [TIAB] OR "accuracy study" [TIAB]) AND (meta-analysis [TIAB] OR scoping [TIAB] OR systematic [TIAB])) OR ("evidence assessment" [TIAB] AND GRADE [TIAB]) OR ("evidence gap" [TIAB:~2] AND "gap map" [TIAB:~0]) OR "evidence mapping" [TIAB] OR "evidence review" [TIAB] OR "exploratory review" [TIAB] OR "framework synthesis" [TIAB] OR "mapping review" [TIAB:~1] OR "meta epidemiological" [TIAB] OR "meta ethnographic" [TIAB:~0] OR metaethnographic [TIAB] OR "meta ethnography" [TIAB:~0] OR metaethnography [TIAB] OR "meta interpretation" [TIAB:~1] OR "meta narrative" [TIAB:~1] OR "meta review" [TIAB:~1] OR "meta study" [TIAB:~1] OR "meta synthesis" [TIAB:~0] OR metasynthesis [TIAB] OR "meta summary" [TIAB:~1] OR "meta theory" [TIAB:~1] OR "methodological review" [TIAB:~1] OR "methodology review" [TIAB:~1] OR ("mixed methods" [TIAB:~0] AND "methods review" [TIAB:~1]) OR ("mixed methods" [TIAB:~0] AND "methods synthesis" [TIAB:~1]) OR "narrative synthesis" [TIAB:~1] OR "overview reviews" [TIAB:~4] OR ("PRISMA" [TIAB] AND (guideline [TIAB] OR guidelines [TIAB] OR preferred [TIAB] OR reporting [TIAB] OR requirements [TIAB])) OR "PRISMA-P" [TIAB:~0] OR "prognostic review" [TIAB:~1] OR "psychometric review" [TIAB:~1] OR ("qualitative evidence" [TIAB:~0] AND "evidence synthesis" [TIAB:~0]) OR ("qualitative research" [TIAB:~0] AND "research synthesis" [TIAB:~0]) OR ("rapid evidence" [TIAB:~0] AND "evidence assessment" [TIAB:~0]) OR "rapid realist" [TIAB:~0] OR "rapid review" [TIAB:~1] OR "rapid reviews" [TIAB:~1] OR "realist review" [TIAB:~1] OR ("review economic" [TIAB:~1] AND ("economic evaluation" [TIAB:~1] OR "economic evaluations" [TIAB:~1])) OR "review reviews"		

No.	Query	Filters	Search Details	Results	Time
			[TIAB:~1] OR "realist syntheses" [TIAB:~1] OR "realist synthesis" [TIAB:~1] OR "scoping review" [TIAB:~2] OR "scoping reviews" [TIAB:~2] OR "scoping studies" [TIAB:~2] OR "scoping study" [TIAB:~2] OR "systematic evidence map" [TIAB] OR "systematic mapping" [TIAB:~2] OR "systematic literature" [TIAB:~1] OR "systematic Medline" [TIAB:~2] OR "systematic PubMed" [TIAB:~2] OR "systematic review" [TIAB:~2] OR "systematic reviews" [TIAB:~2] OR "systematical review" [TIAB:~1] OR "systematical reviews" [TIAB:~2] OR "systematically identified" [TIAB:~1] OR "systematically review" [TIAB:~1] OR "systematically reviewed" [TIAB:~1] OR "systematized review" [TIAB:~1] OR "umbrella review" [TIAB:~2] OR "umbrella reviews" [TIAB:~2] OR "meta-analysis as topic"[MESH:NOEXP] OR Meta-Analysis[PT] OR "network meta-analysis"[mesh:noexp] OR "indirect comparison"[TIAB:~1] OR meta analyses[TIAB] OR meta analysis[TIAB] OR meta analytic[TIAB] OR meta analytical[TIAB] OR meta analytics[TIAB] OR meta analyze[TIAB] OR meta analyzed[TIAB] OR metaanalyses[TIAB] OR metaanalysis[TIAB] OR metaanalytic[TIAB] OR metaanalyze[TIAB] OR metaanalyzed[TIAB] OR "network comparison"[TIAB:~1] OR "network meta analyses"[TIAB] OR "network meta analysis"[TIAB] OR "network metaanalyses"[TIAB] OR "network metaanalysis"[TIAB] OR (systematic[tiab] AND (meta regression[TIAB] OR metaregression[TIAB]))))		
9	#1 AND #8 (*Antibiotic prophylaxis specific to leptospirosis*)			39	20:38:45
8	#6 AND #7 (*Antibiotic prophylaxis subset*)			10,351	20:36:41
7	(Post-exposure prophylaxis) OR (Antibiotic prophylaxis) OR (Chemoprophylaxis) OR (Prophylactic treatment)		(((((((post exposure prophylaxis[MeSH Terms]) OR (antibiotic prophylaxis[MeSH Terms])) OR (chemoprophylaxis[MeSH Terms])) OR (PEP)) OR (antibiotic prophylaxis)) OR (chemoprophylaxis)) OR (prophylactic treatment)) OR (post-exposure prophylaxis)	160,258	20:35:12
6	#2 OR #3 OR #4 OR #5 (*All antibiotics*)			328,531	20:32:20
5	(Doxycycline)		(Doxycycline[MeSH] OR Doxycycline)	22,324	20:31:10
4	(Macrolide) OR (Azithromycin)		(Macrolides[MeSH] OR Macrolide OR Azithromycin[MeSH] OR Azithromycin)	141,637	20:30:05
3	(Cephalosporin) OR (Ceftriaxone) OR (Cefotaxime)		(Cephalosporins[MeSH] OR Cephalosporin OR Ceftriaxone[MeSH] OR Ceftriaxone OR Cefotaxime[MeSH] OR Cefotaxime)	75,156	20:28:57
2	(Penicillin) OR (Amoxicillin)		(Penicillins[MeSH] OR Penicillin OR Amoxicillin[MeSH] OR Amoxicillin)	130,939	20:26:51
1	(Leptospirosis) OR (Leptospira) + infection, prevention, exposure		(Leptospirosis[MeSH] OR Leptospira[MeSH] OR Leptospirosis OR Leptospira OR "Leptospira infection" OR "Leptospirosis prevention" OR "Leptospira exposure")	14,543	20:24:38

Detailed Search: EMBASE

Date of Search: 12 November 2024; Updated: 08 May 2025

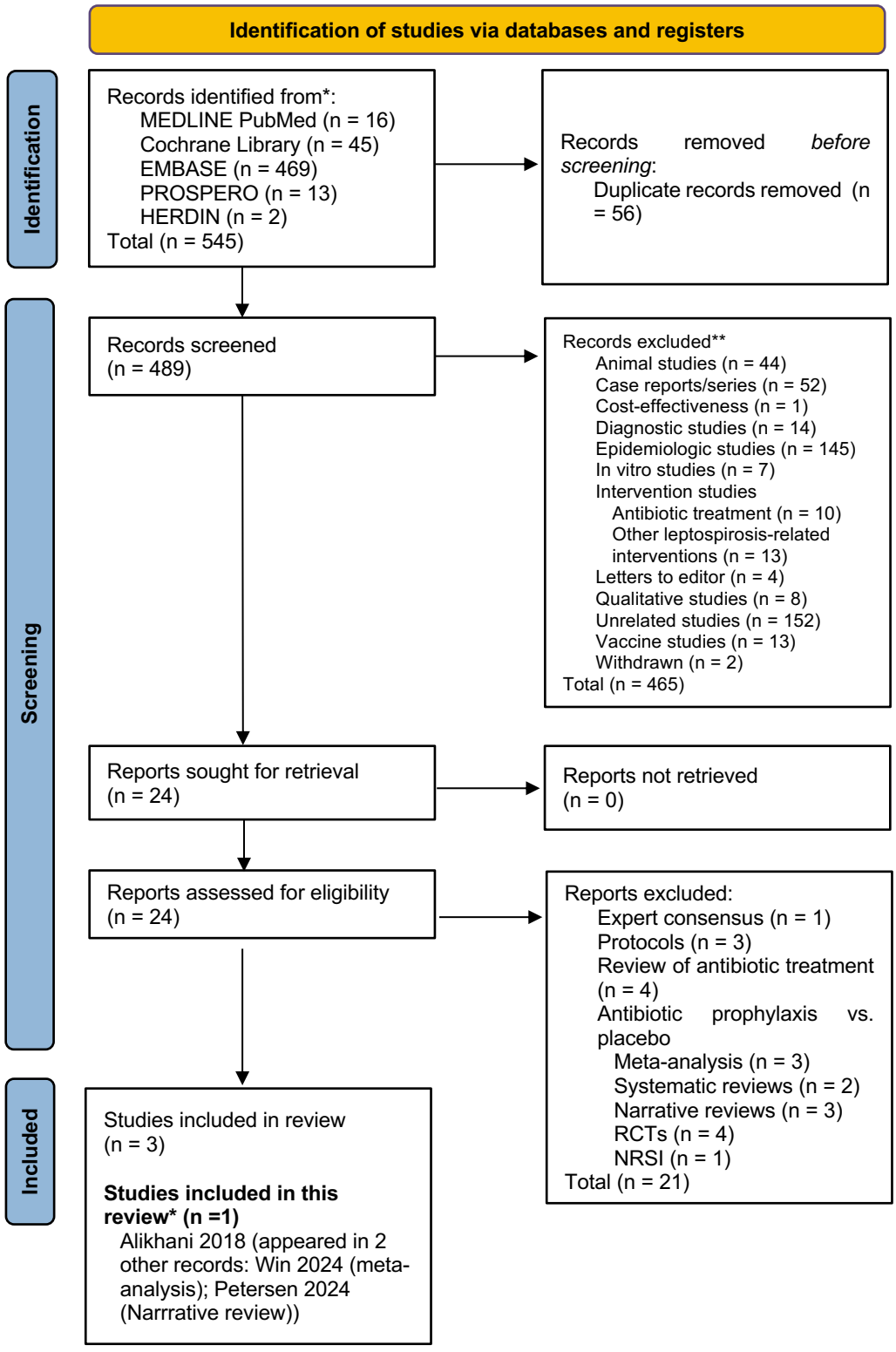
No.	Query	Results
#12	#9 AND ('case control study'/de OR 'case report'/de OR 'clinical trial'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'cross sectional study'/de OR 'longitudinal study'/de OR 'observational study'/de OR 'prospective study'/de OR 'retrospective study'/de) NOT 'nonhuman'/de	383
#11	#8 AND #4 AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim)	26
#10	#8 AND #4 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)	60
#9	#8 AND #4	2,085
#8	#6 OR #5 OR #7	3,962,962
#7	prophyla*:ab,ti OR prevent*:ab,ti OR protec*:ab,ti OR premedic*:ab,ti OR chemoprophyla*:ab,ti	3,944,480
#6	'prophylaxis':ab,ti	192,585
#5	'antibiotic prophylaxis'	49,030
#4	#1 OR #2 OR #3	17,586
#3	'leptospirosis'/exp OR 'leptospirosis' OR 'leptospirosis':ab,ti	15,158
#2	'leptospira':ab,ti	7,989
#1	'leptospira interrogans':ab,ti	2,368

Detailed Search: Cochrane CENTRAL

Date of Search: 12 November 2024; Updated: 07 May 2025

ID	Search	Hits
#1	MeSH descriptor: [Leptospirosis] explode all trees	44
#2	leptospirosis	112
#3	leptospira	33
#4	leptospira infection	17
#5	leptospirosis prevention	34
#6	leptospira exposure	17
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	116
#8	MeSH descriptor: [Post-Exposure Prophylaxis] explode all trees	132
#9	antibiotic prophylaxis	6012
#10	chemoprophylaxis	1709
#11	prophylactic treatment	11771
#12	#8 OR #9 OR #10 OR #11	18301
#13	#7 AND #12	15

PRISMA Flow Diagram



Included and Excluded Studies

Characteristics of Included Studies

Study	Study design	Setting	Trial Aim	Population	Intervention	Control	Outcome
Alikhani 2018[3]	RCT, double-blind, placebo-controlled	Iran (single center)	Pre-exposure prophylaxis	n = 200 *Age:* 18-65 years *Characteristics:* Residing in endemic area and who were supposed to work in the paddy field after giving consent	*Experimental group 1* (n = 68): **azithromycin** 500 mg weekly *Experimental group 2* (n = 71): **doxycycline** 200 mg weekly	*Control group* (n = 61): **placebo** *Note:* **Azithromycin vs. doxycycline** can be derived from the results.	*Primary outcomes:* fever, body pain, red eye, calf pain, icterus Time point: 0, 6, 12 weeks for IgG and 2nd week after developing disease for IgM *Secondary outcomes:* nausea, vomiting, esophagitis, photosensitivity Time point: drug consumption periods

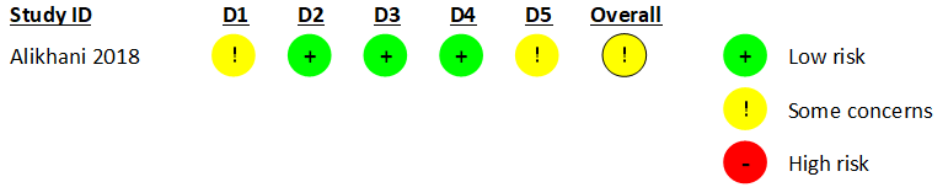
Characteristics of Excluded Studies

Study	Study design	Setting	Trial Aim	Population	Intervention	Control	Outcome
Gonsalez 1998[4]	RCT	Brazil	Post-exposure prophylaxis	n = 82 *Age:* 18-74 years *Characteristics:* Residents in an area at high risk for flooding	*Experimental group* (n = 40): **doxycycline** 200 mg once at first bleeding	*Control group* (n = 42): **placebo**	*Laboratory-confirmed leptospirosis* Time point: 0 and 45 days for IgG measured by enzyme immunoassay *Clinical case of leptospirosis:* fever, chills, myalgia, nausea, vomiting, abdominal pain, conjunctivitis, and headache accompanied by neck stiffness Time point: period immediately after exposure to flooding
Illangasekera 2008[5]	RCT	Sri Lanka (two centers)	Post-exposure prophylaxis	n = 800 *Age:* 20-80 years *Characteristics:* Residents in high transmission area	*Experimental group* (n = 292): **penicillin** 250 mg in 2 tablets twice a day for 1 month	*Control group* (n = 310): **placebo**	*Laboratory-confirmed leptospirosis* Time point: paired blood samples taken 10 days apart for *Leptospira* serology by microagglutination test *Clinical case of leptospirosis* Time point: during and after the study period using checklist of symptoms of leptospirosis
Sehgal 2000[6]	RCT	India	Pre-exposure prophylaxis	n = 1,025 *Age:* 10-40 years and above *Characteristics:* Residents living in high endemic area	*Experimental group* (n = 513): **doxycycline** 100 mg in 2 doses	*Control group* (n = 512): **placebo** (vitamin B complex)	*Leptospirosis case* Time point: day 0, after 6 weeks, after 12 weeks using the microagglutination test; isolation of leptospirosis was performed for all participants who had febrile illness during the trial *Mortality, febrile illness, and adverse events* Time point: during the trial period
Takafuji 1984[7]	RCT	Panama	Pre-exposure prophylaxis	n = 940 *Age:* not reported *Characteristics:* Volunteer soldiers present at a	*Experimental group* (n = 469): **doxycycline** 200 mg at the time of	*Control group* (n = 471): **placebo**	*Laboratory-confirmed case* Time point: 1 week before travel to Panama, within 1 week after their return to the US, and approximately 4-6 weeks later

Study	Study design	Setting	Trial Aim	Population	Intervention	Control	Outcome
				military installation in Panama Canal region	enrollment in the trial; the same dose was taken at the beginning of each subsequent week of training and at the completion of the exercise immediately before departure from Panama		for leptospiral antibody by microagglutination test and culture *Specific symptoms:* fever, chills, headache, neck stiffness, dizziness, back pain, muscle aches, joint pain, tiredness, nausea, vomiting, abdominal pain, diarrhea, eye redness or pain, photophobia, rash, cough, and nasal congestion Time point: at the end of each week's training for 3 weeks
Chusri 2014[8]	NRSI	Thailand	Post-exposure prophylaxis	n = 663 *Age:* 18 years or above *Characteristics:* Exposed to flood water since a determined start date; examined for skin disruption	*Experimental group* (n = 619): **doxycycline** 200 mg as single dose upon enrollment	*Control group* (n = 44): **no intervention**	*Laboratory-confirmed case* Time point: Two serums obtained at least 2 weeks apart, observing for fourfold or greater increase in IFAT for specific leptospiral IgG and confirmed with a fourfold or greater increase in leptospiral agglutination titer with MCAT *Specific symptoms:* fever, headache, chills, myalgia, conjunctival suffusion, meningitis, jaundice, or renal insufficiency Time point: at the first date of assessment until second date of assessment (14-28 days interval)

Risk of Bias Assessment

Risk of bias assessment of the included randomized controlled trial using the RoB2 tool



RoB2 Domain	Judgment	Explanation
D1 Randomization process	Some concerns	Randomization was conducted but not described in detail. Baseline balance is reassuring but insufficient to confirm low risk.
D2 Deviations from intended interventions	Low risk	Blinding and protocol adherence were likely adequate. No deviations that affected outcomes were reported.
D3 Missing outcome data	Low risk	Minimal dropout. Outcome data were reported for nearly all participants.
D4 Measurement of the outcome	Low risk	Double-blind design and uniform assessment across arms. IgG/IgM ELISA was used consistently.
D5 Selection of the reported result	Some concerns	Lack of access to the protocol raises concerns for selective reporting. SAEs were not reported or pre-specified.

GUIDELINE QUESTION 5: Should azithromycin, cephalosporin, or amoxicillin be used as post-exposure prophylaxis for leptospirosis in children <8 years of age and pregnant women?

Research Question: Among children aged <8 years and pregnant women, how effective and safe are antibiotics as post-exposure prophylaxis in preventing leptospirosis?	
Population	Children <8 years old, pregnant women
Intervention / Treatment	Azithromycin, cephalosporin, amoxicillin
Comparator	Azithromycin, cephalosporin, amoxicillin, no post-exposure prophylaxis
Outcomes	Incidence of leptospirosis infection; safety (any adverse events, serious adverse events)
Subgroups (if any)	Children<8 years old; pregnant women
Methods	RCTs; NRSIs

Evidence Reviewers: Dr. Krizia Joy A. Co, Mr. Howell Henrian G. Bayona
Date of Last Search: February 17, 2025

Statement of the Evidence

Based on two observational studies, the effect of azithromycin or amoxicillin as post-exposure prophylaxis on reducing leptospirosis incidence as well as its safety among children <8 years old and pregnant women is very uncertain.

The overall certainty of evidence is **very low**.

Review Methods

A systematic search was done from November 13, 2024 to February 17, 2025 using Embase and PubMed with combined MeSH and free text search using the terms leptospirosis, *leptospira*, infection, prevention, and chemoprophylaxis. From these, filters for children and pregnant women were applied to narrow the search. We also searched for ongoing studies in the NIH clinicaltrials.gov and other trial registries, local studies from the Philippine Health Research Registry, and preprints from medrxiv, chinaxiv and biorxiv.

The studies that included pregnant women and/or children <8 years old which indicated the post-exposure prophylactic antibiotic used were included. Outcomes of interest included incidence of leptospirosis and adverse events. There were no randomized clinical trials identified, hence observational studies were considered. The ROBINS-I V2 assessment tool was used to assess the risk of bias for the observational studies.

Recommendations from Other Groups

For children

In 2019, the Philippine Pediatric Society and Pediatric Infectious Disease Society of the Philippines published strongly recommended the use of oral penicillin as post-exposure prophylaxis for children in high-transmission areas, despite the absence of studies specifically on children. The 2017 DOH National Antibiotic Guideline (NAG) also recommended amoxicillin or azithromycin as second-line regimens for children. The reviewed study on azithromycin used a singular dosing regimen for azithromycin for children compared to the weight-based dose included in the NAG, whereas the reviewed study for amoxicillin did not specify any dose.

For pregnant women

No specific recommendations are available for pregnant women from local guidelines. The 2011 Ministry of Health in Malaysia guideline recommended azithromycin for this population.

Group or Agency	Recommendations for Alternative Post-exposure Prophylaxis		Strength of recommendation and certainty of evidence
	Pregnant women	Children	
Ministry of Health Malaysia[15] (2011)	Azithromycin 1 g on day 1 then 500 mg daily for 2 days	*No recommendation*	Not indicated
Philippine Pediatric Society – Pediatric Infectious Disease Society of the Philippines[16] (2019)	–	**Oral penicillin** may be used for post-exposure prophylaxis in children to prevent symptomatic leptospirosis in high transmission areas but there are no studies in children.	Strong recommendation, very low certainty
Department of Health- National Antibiotic Guideline[17] (2017)	*No specific recommendation for pregnant women*	**Second line regimens:** **Amoxicillin** 50mg/kg/d q8h x 3-5d (Max: 500mg q8h) OR **Azithromycin** 10mg/kg x 1 dose (Max: 500 mg) If children (no age specified) are exposed for more than 7 days, the dose should be repeated after 1 week.	Not indicated*

*Cited an earlier version of the PIDSP guidance (2012)[11] as reference, rationale stated are the following:

a. Azithromycin: Efficacy for prevention of leptospirosis was seen in-vitro and animal models
b. Amoxicillin: No clinical trial for prevention of leptospirosis, but amoxicillin is a known alternative for the treatment of disease. Dose is for 3-5 days due to the very short half-life.

Ongoing Studies and Research Gaps

There are no ongoing studies identified during the search. There is a need to perform well designed interventional studies among children <8 years old and pregnant women to determine the benefits and risks associated with post-exposure prophylaxis. Such studies should also monitor for adverse outcomes for such interventions to determine the risk-benefit profile of chemoprophylaxis in this population.

[15] Disease Control Division D of PHM of H– Malaysia. Guidelines For The Diagnosis, Management, Prevention And Control Of Leptospirosis In Malaysia [Internet]. [cited 2025 Feb 25]. Available from: https://www.moh.gov.my/moh/images/gallery/Garispanduan/GL_ Leptospirosis%202011.pdf.
[16] Philippine Pediatric Society – Pediatric Infectious Disease Society of the Philippines. Clinical Practice Guidelines on Leptospirosis in Children. 2019. [cited 2025 Feb 25]; Available from: http://www.pidsphil.org/home/wp-content/uploads/2022/03/CPG-OF-LEPTOSPIROSIS-FINAL-VERSION .pdf.
[17] Department of Health. National Antibiotic Guideline 2017. 2017. 16 p.

Search Strategy

Search strategy for children <8 years old

Database	Search Strategy / Search Terms	Date and Time of Search	Results	
			Yield	Eligible
Medline	("leptospirosis"[MeSH Terms] OR "leptospira"[MeSH Terms] OR ("leptospirosis"[MeSH Terms] OR "leptospirosis"[All Fields] OR "leptospiroses"[All Fields]) OR ("leptospira"[MeSH Terms] OR "leptospira"[All Fields] OR "leptospirae"[All Fields] OR "leptospiras"[All Fields]) OR "Leptospira infection"[All Fields] OR "Leptospirosis prevention"[All Fields] OR "Leptospira exposure"[All Fields]) AND (("penicillins"[MeSH Terms] OR ("benzylpenicillins"[All Fields] OR "penicillin g"[MeSH Terms] OR "penicillin g"[All Fields] OR "benzylpenicillin"[All Fields] OR "penicilline"[All Fields] OR "penicillines"[All Fields] OR "penicillins"[MeSH Terms] OR "penicillins"[All Fields] OR "penicillin"[All Fields]) OR "amoxicillin"[MeSH Terms] OR ("amoxicillin"[MeSH Terms] OR "amoxicillin"[All Fields] OR "amoxicilline"[All Fields] OR "amoxicillins"[All Fields]) OR ("cephalosporins"[MeSH Terms] OR ("cephalosporine"[All Fields] OR "cephalosporines"[All Fields] OR "cephalosporins"[MeSH Terms] OR "cephalosporins"[All Fields] OR "cephalosporin"[All Fields]) OR "ceftriaxone"[MeSH Terms] OR ("ceftriaxone"[MeSH Terms] OR "ceftriaxone"[All Fields] OR "ceftriaxon"[All Fields]) OR "cefotaxime"[MeSH Terms] OR ("cefotaxime"[MeSH Terms] OR "cefotaxime"[All Fields] OR "cefotaxim"[All Fields])) OR ("macrolides"[MeSH Terms] OR ("macrolid"[All Fields] OR "macrolides"[MeSH Terms] OR "macrolides"[All Fields] OR "macrolide"[All Fields] OR "macrolids"[All Fields]) OR "azithromycin"[MeSH Terms] OR ("azithromycin"[MeSH Terms] OR "azithromycin"[All Fields] OR "azithromycine"[All Fields] OR "azithromycin s"[All Fields])) OR ("doxycycline"[MeSH Terms] OR ("doxycycline"[MeSH Terms] OR "doxycycline"[All Fields] OR "doxycyclin"[All Fields]))) AND ("post exposure prophylaxis"[MeSH Terms] OR "antibiotic prophylaxis"[MeSH Terms] OR "chemoprevention"[MeSH Terms] OR "PEP"[All Fields] OR ("antibiotic prophylaxis"[MeSH Terms] OR ("antibiotic"[All Fields] AND "prophylaxis"[All Fields]) OR "antibiotic prophylaxis"[All Fields]) OR ("chemoprevention"[MeSH Terms] OR "chemoprevention"[All Fields] OR "chemoprophylaxis"[All Fields] OR "chemoprophylaxy"[All Fields]) OR (("condoms"[MeSH Terms] OR "condoms"[All Fields] OR "prophylactic"[All Fields] OR "prophylactically"[All Fields] OR "prophylactics"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "treatments"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "treatment s"[All Fields])) OR ("post exposure prophylaxis"[MeSH Terms] OR ("post exposure"[All Fields] AND "prophylaxis"[All Fields]) OR "post exposure prophylaxis"[All Fields] OR ("post"[All Fields] AND "exposure"[All Fields] AND "prophylaxis"[All Fields]) OR "post exposure prophylaxis"[All Fields]))) **Filters** (population): pregnant **Filters** (study type): Systematic reviews, meta-analysis, traditional reviews, clinical trials, quasi-experimental studies	February 17, 2025 2:50PM	1	1
CENTRAL	#1 Leptospirosis #2 antibiotic prophylaxis #3 post-exposure prophylaxis #4 #2 OR #3 #5 #1 AND #4 #6 pregnancy #7 pregnant #8 #6 OR #7 #9 #5 AND #8	February 17, 2025 3:33PM	0	0
EMBASE	**#21** #13 AND 'human'/de **#20** #19 AND #9	November 14, 2024	19	2

Database	Search Strategy / Search Terms	Date and Time of Search	Results	
			Yield	Eligible
	#19 #18 OR #17 OR #16 OR #15 OR #14 **#18** gravidism:ti,ab **#17** 'maternity':ti,ab **#16** 'expectant mother':ti,ab **#15** 'pregnant woman' **#14** 'pregnancy':ti,ab **#13** #8 AND #4 AND ([embryo]/lim OR [fetus]/lim OR [newborn]/lim OR [infant]/lim OR [child]/lim OR [preschool]/lim OR [school]/lim) **#12** #9 AND ('case control study'/de OR 'case report'/de OR 'clinical trial'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'cross sectional study'/de OR 'longitudinal study'/de OR 'observational study'/de OR 'prospective study'/de OR 'retrospective study'/de) NOT 'nonhuman'/de **#11** #8 AND #4 AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) **#10** #8 AND #4 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim) **#9** #8 AND #4 **#8** #6 OR #5 OR #7 **#7** prophyla*:ab,ti OR prevent*:ab,ti OR protec*:ab,ti OR premedic*:ab,ti OR chemoprophyla*:ab,ti **#6** 'prophylaxis':ab,ti **#5** 'antibiotic prophylaxis' **#4** #1 OR #2 OR #3 **#3** 'leptospirosis'/exp OR 'leptospirosis' OR 'leptospirosis':ab,ti **#2** 'leptospira':ab,ti **#1** 'leptospira interrogans':ab,ti			
Philippine Health Research Registry	Leptospirosis	February 17, 2025 3:15PM	1	0
ClinicalTrials.gov	Leptospirosis	February 17, 2025 3:30PM	1	0
Chinese Clinical Trial Registry	Leptospirosis	February 17, 2025 3:35PM	0	0
EU Clinical Trials Register	Leptospirosis	February 17, 2025 3:40PM	1	0
Republic of Korea - Clinical Research Information Service	Leptospirosis	February 17, 2025 3:45PM	0	0
Japan Primary Registries	Leptospirosis	February 17, 2025	0	0

Database	Search Strategy / Search Terms	Date and Time of Search	Results	
			Yield	Eligible
Network/ NIPH Clinical Trials Search		3:50PM		
CenterWatch	Leptospirosis	February 17, 2025 3:55PM	5	0
chinaxiv.org	Leptospirosis	February 17, 2025 4:00PM	0	0
Medrxiv.org	Leptospirosis and prophylaxis	February 17, 2025 4:05PM	10	0
Biorxiv.org	Leptospirosis and prophylaxis	February 17, 2025 4:10PM	6	0

Search strategy for children <8 years old

Database	Search Strategy / Search Terms	Date and Time of Search	Results	
			Yield	Eligible
Medline	("leptospirosis"[MeSH Terms] OR "leptospira"[MeSH Terms] OR ("leptospirosis"[MeSH Terms] OR "leptospirosis"[All Fields] OR "leptospiroses"[All Fields]) OR ("leptospira"[MeSH Terms] OR "leptospira"[All Fields] OR "leptospirae"[All Fields] OR "leptospiras"[All Fields]) OR "Leptospira infection"[All Fields] OR "Leptospirosis prevention"[All Fields] OR "Leptospira exposure"[All Fields]) AND (("penicillins"[MeSH Terms] OR ("benzylpenicillins"[All Fields] OR "penicillin g"[MeSH Terms] OR "penicillin g"[All Fields] OR "benzylpenicillin"[All Fields] OR "penicilline"[All Fields] OR "penicillines"[All Fields] OR "penicillins"[MeSH Terms] OR "penicillins"[All Fields] OR "penicillin"[All Fields]) OR "amoxicillin"[MeSH Terms] OR ("amoxicillin"[MeSH Terms] OR "amoxicillin"[All Fields] OR "amoxicilline"[All Fields] OR "amoxicillins"[All Fields]) OR ("cephalosporins"[MeSH Terms] OR ("cephalosporine"[All Fields] OR "cephalosporines"[All Fields] OR "cephalosporins"[MeSH Terms] OR "cephalosporins"[All Fields] OR "cephalosporin"[All Fields]) OR "ceftriaxone"[MeSH Terms] OR ("ceftriaxone"[MeSH Terms] OR "ceftriaxone"[All Fields] OR "ceftriaxon"[All Fields]) OR "cefotaxime"[MeSH Terms] OR ("cefotaxime"[MeSH Terms] OR "cefotaxime"[All Fields] OR "cefotaxim"[All Fields])) OR ("macrolides"[MeSH Terms] OR ("macrolid"[All Fields] OR "macrolides"[MeSH Terms] OR "macrolides"[All Fields] OR "macrolide"[All Fields] OR "macrolids"[All Fields]) OR "azithromycin"[MeSH Terms] OR ("azithromycin"[MeSH Terms] OR "azithromycin"[All Fields] OR "azithromycine"[All Fields] OR "azithromycins"[All Fields])) OR ("doxycycline"[MeSH Terms] OR ("doxycycline"[MeSH Terms] OR "doxycycline"[All Fields] OR "doxycyclin"[All Fields]))) AND ("post exposure prophylaxis"[MeSH Terms] OR "antibiotic prophylaxis"[MeSH Terms] OR "chemoprevention"[MeSH Terms] OR "PEP"[All Fields] OR ("antibiotic prophylaxis"[MeSH Terms] OR ("antibiotic"[All Fields] AND "prophylaxis"[All Fields]) OR "antibiotic prophylaxis"[All Fields]) OR ("chemoprevention"[MeSH Terms] OR "chemoprevention"[All Fields] OR "chemoprophylaxis"[All Fields] OR "chemoprophylaxy"[All Fields]) OR (("condoms"[MeSH Terms] OR "condoms"[All Fields] OR "prophylactic"[All Fields] OR "prophylactically"[All Fields] OR "prophylactics"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "treatments"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "treatment s"[All Fields])) OR ("post exposure prophylaxis"[MeSH Terms] OR ("post exposure"[All Fields] AND "prophylaxis"[All Fields]) OR "post exposure prophylaxis"[All Fields] OR ("post"[All Fields] AND	February 17, 2025 2:50PM	1	1

<table>
<tr><th>Database</th><th>Search Strategy / Search Terms</th><th>Date and Time of Search</th><th colspan="2">Results</th></tr>
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<tr><td></td><td>"exposure"[All Fields] AND "prophylaxis"[All Fields]) OR "post exposure prophylaxis"[All Fields])))

Filters (population): pregnant
Filters (study type): Systematic reviews, meta-analysis, traditional reviews, clinical trials, quasi-experimental studies</td><td></td><td></td><td></td></tr>
<tr><td>CENTRAL</td><td>#1 Leptospirosis
#2 antibiotic prophylaxis
#3 post-exposure prophylaxis
#4 #2 OR #3
#5 #1 AND #4
#6 pregnancy
#7 pregnant
#8 #6 OR #7
#9 #5 AND #8</td><td>February 17, 2025 3:33PM</td><td>0</td><td>0</td></tr>
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<tr><td>#19</td><td>#18 OR #17 OR #16 OR #15 OR #14</td></tr>
<tr><td>#18</td><td>gravidism:ti,ab</td></tr>
<tr><td>#17</td><td>'maternity':ti,ab</td></tr>
<tr><td>#16</td><td>'expectant mother':ti,ab</td></tr>
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<tr><td>#13</td><td>#8 AND #4 AND ([embryo]/lim OR [fetus]/lim OR [newborn]/lim OR [infant]/lim OR [child]/lim OR [preschool]/lim OR [school]/lim)</td></tr>
<tr><td>#12</td><td>#9 AND ('case control study'/de OR 'case report'/de OR 'clinical trial'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'cross sectional study'/de OR 'longitudinal study'/de OR 'observational study'/de OR 'prospective study'/de OR 'retrospective study'/de) NOT 'nonhuman'/de</td></tr>
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<tr><td>#10</td><td>#8 AND #4 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)</td></tr>
<tr><td>#9</td><td>#8 AND #4</td></tr>
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<tr><td>#7</td><td>prophyla*:ab,ti OR prevent*:ab,ti OR protec*:ab,ti OR premedic*:ab,ti OR chemoprophyla*:ab,ti</td></tr>
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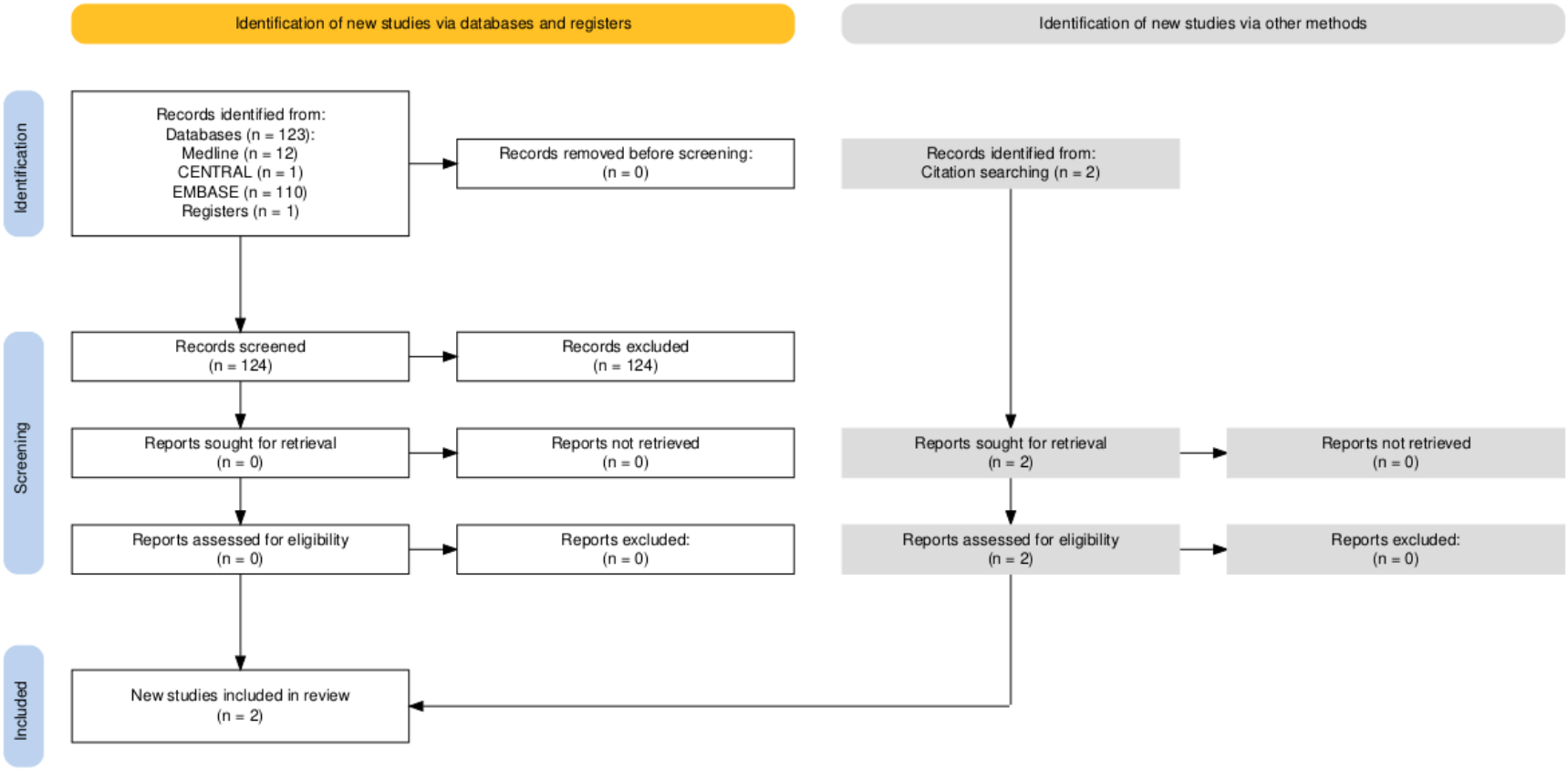
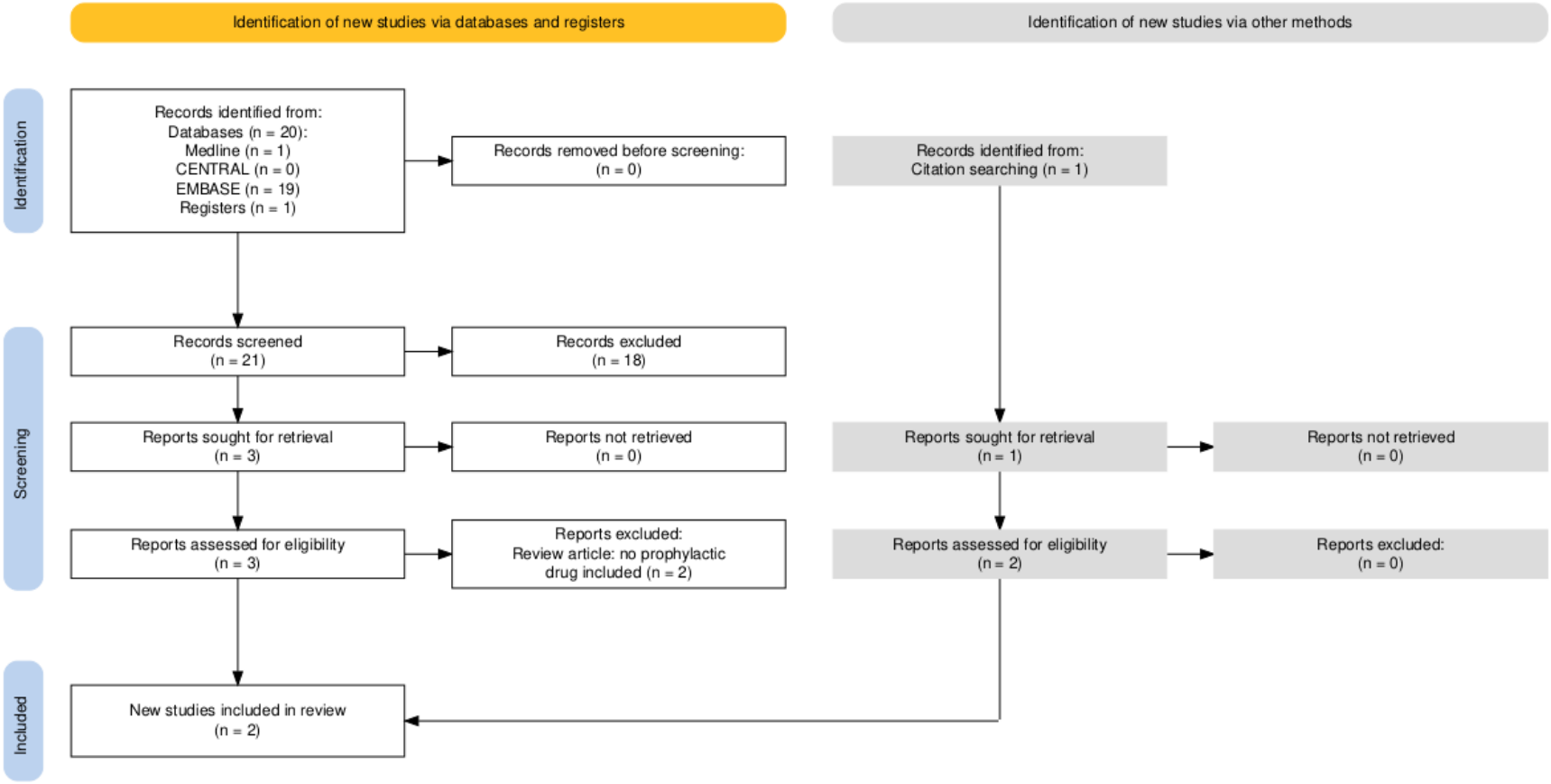
Database	Search Strategy / Search Terms	Date and Time of Search	Results	
			Yield	Eligible
Philippine Health Research Registry	Leptospirosis	February 17, 2025 3:15PM	1	0
ClinicalTrials.gov	Leptospirosis	February 17, 2025 3:30PM	1	0
Chinese Clinical Trial Registry	Leptospirosis	February 17, 2025 3:35PM	0	0
EU Clinical Trials Register	Leptospirosis	February 17, 2025 3:40PM	1	0
Republic of Korea - Clinical Research Information Service	Leptospirosis	February 17, 2025 3:45PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Leptospirosis	February 17, 2025 3:50PM	0	0
CenterWatch	Leptospirosis	February 17, 2025 3:55PM	5	0
chinaxiv.org	Leptospirosis	February 17, 2025 4:00PM	0	0
Medrxiv.org	Leptospirosis and prophylaxis	February 17, 2025 4:05PM	10	0
Biorxiv.org	Leptospirosis and prophylaxis	February 17, 2025 4:10PM	6	0

PRISMA Flow Diagrams

PRISMA Flow diagram for children <8 years old



PRISMA Flow diagram for pregnant women



Included Studies

Characteristics of Included Studies

Author Year	Study design	Country	Number of patients	Population	Intervention Group(s)	Control	Outcomes
Supe 2018	Retrospective cohort	India	4465[a]	Children <8 years old	**Low-risk**[b] Azithromycin 200mg syrup single dose or 250 mg tablet single dose within 24–72 hours **Moderate-risk**[c] Azithromycin 200mg syrup or 250mg tablet once daily for 3 days	None	PCR confirmed Leptospirosis (period of 3 weeks after the flood)
			359[a]	Pregnant	**Low-risk**[b] Azithromycin 500mg tablet within 24–72 hours **Moderate-risk**[c] Azithromycin 500mg tablet once daily for 3 days	None	PCR confirmed Leptospirosis (period of 3 weeks after the flood)
DeChet 2012	Retrospective cohort	Guyana	Not reported	Children <8 years old, Pregnant, Breastfeeding exposed to flood waters	Weekly 5-day course of amoxicillin	None	Suspected/ Probable/ Confirmed Leptospirosis (period of 6 weeks after the flood)

[a]Part of the total 156,934 adults given prophylaxis by paramedical staff; identified after screening 6,714,210 citizens of Mumbai

[b]**Low-risk:** with history of one-time wading in flooded or contaminated water without wounds, cuts or open lesions of the skin

[c]**Moderate-risk**: with history of one-time wading in flooded or contaminated water, and the presence of wounds, cuts or open lesions of the skin or accidental ingestion of contaminated water

Quality Assessment of Included Studies

Author Year	Study design	Overall assessment	Remarks
Supe 2018	Retrospective cohort	Critical risk of bias	No further assessment required based on ROBINS-I V2 assessment tool due to 1) No adjustment for confounders done The method for measuring the outcome is inappropriate (the measured outcome is not limited to the study population, outcomes were not stratified to pregnant/ children)
DeChet 2012	Retrospective cohort	Critical risk of bias	

GUIDELINE QUESTION 6: Should steroids, cyclophosphamide, or combination of both be used to prevent pulmonary hemorrhage and acute kidney injury in cases of severe leptospirosis?

Research Question: Among patients with severe leptospirosis, how effective and safe is steroid, cyclophosphamide, or a combination of both drugs in preventing pulmonary hemorrhage and acute kidney injury?	
Population	Patients with severe leptospirosis; any age
Intervention / Treatment	Steroid, cyclophosphamide, or steroid plus cyclophosphamide combination
Comparator	Steroid, cyclophosphamide, steroid plus cyclophosphamide combination, or standard of care
Outcomes	Incidence of pulmonary hemorrhage; incidence of acute kidney injury; safety
Subgroups (if any)	Pediatric population, adult population
Methods	RCTs; NRSI

Evidence Reviewers: Dr. Emilio Q. Villanueva III, Mr. Howell Henrian G. Bayona, Mr. Kerwyn Jim C. Chan
Date of Last Search: January 16, 2025

Statement of the Evidence

Among patients with severe leptospirosis, prednisolone may have little to no effect in preventing pulmonary hemorrhage and acute kidney injury. No evidence was found regarding its safety. There were no evidence found for efficacy and safety of other types of steroid and cyclophosphamide in preventing pulmonary hemorrhage, and acute kidney injury.

The overall certainty of evidence is **very low**.

Review Methods

A systematic search was done from the date of the database's inception until January 16, 2025 using Medline, and Central with a combined MeSH and free text search terms.

This review included one (1) randomized clinical trial (RCT) that compared the efficacy of prednisolone against standard antibiotic care. Outcomes of interest included incidence of pulmonary hemorrhage and acute kidney injury. The study was assessed using the Cochrane risk-of-bias tool for randomized trials version 2 (RoB-2).

Effect measures were presented as risk ratios. Certainty of evidence was determined using the GRADE approach and judgments were summarized using the GRADEPro software.

During the screening and eligibility assessment, it was observed that most studies examining steroid and cyclophosphamide interventions in patients with severe leptospirosis focused on populations with existing pulmonary and renal complications. Likewise, mortality was the primary outcome measure across these studies. However, these studies were not included in this review to strictly follow the intent of this guideline question.

Recommendations from Other Groups

The DOH Guidelines for Leptospirosis for Hospitals 2019, suggested the use of methylprednisolone 500 mg intravenously per day for 3 days for patients at risk of pulmonary hemorrhage or patients already with renal failure, while the use of cyclophosphamide 1g intravenously as single dose after any episode of hemoptysis or post-hemodialysis.

Group or Agency	Recommendation	Strength of Recommendation/ Certainty of Evidence
DOH Guidelines for Leptospirosis for Hospitals (2019)	**Methylprednisolone** Suggests the use of methylprednisolone 500 mg IV/day for 3 days for patients at risk of pulmonary hemorrhage or patients already with renal failure.	Weak Recommendation
	Cyclophosphamide Suggests the use of cyclophosphamide 1g IV as single dose after any episode of hemoptysis or post-HD.	Weak Recommendation

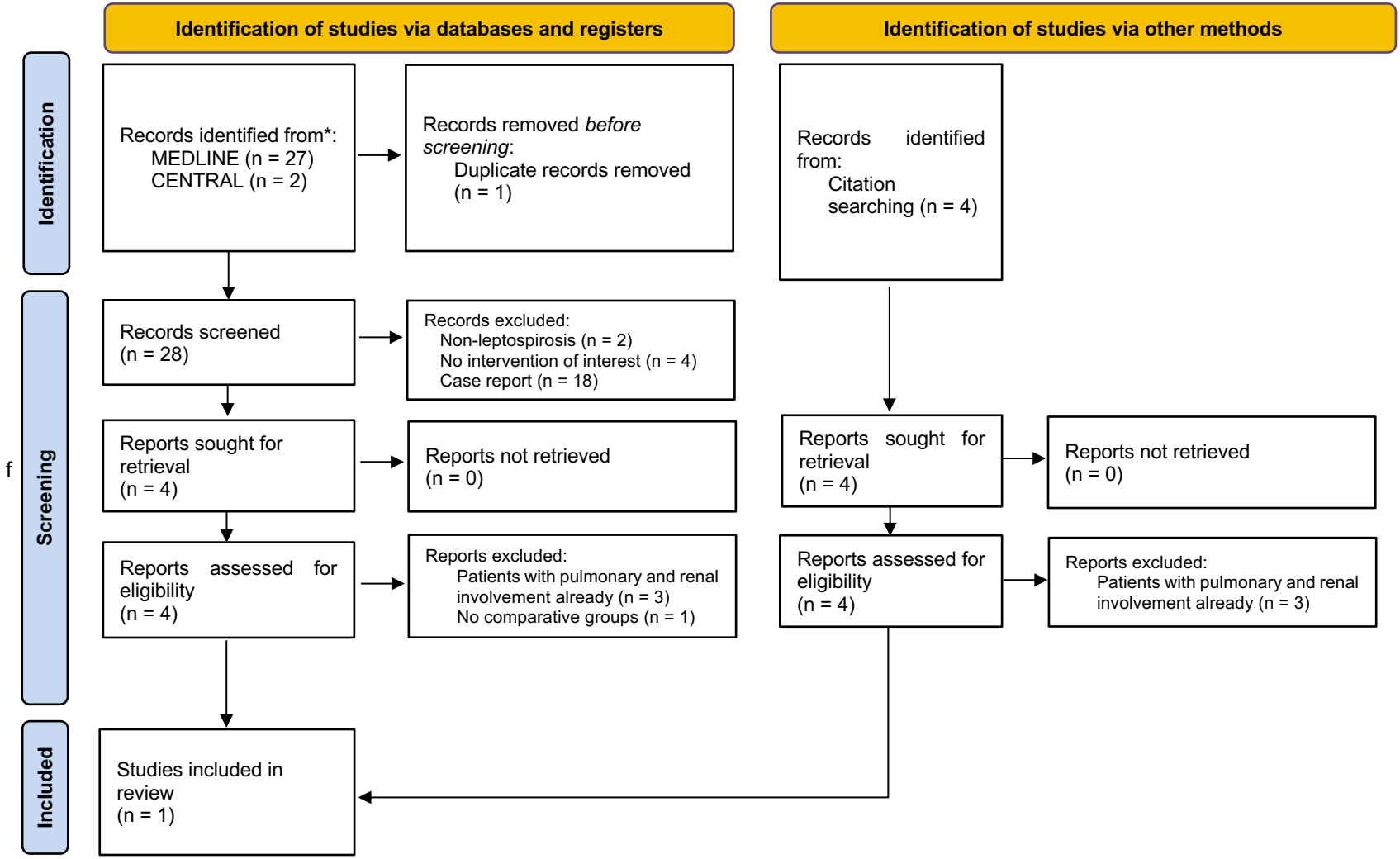
Ongoing Studies and Research Gaps

No ongoing studies were identified on the topic.

Search Strategy

Database searched	Search strategy (syntax used for searching)	Yield
MEDLINE	("sever"[All Fields] OR "severe"[All Fields] OR "severed"[All Fields] OR "severely"[All Fields] OR "severer"[All Fields] OR "severes"[All Fields] OR "severing"[All Fields] OR "severities"[All Fields] OR "severity"[All Fields] OR "severs"[All Fields]) AND ("leptospirosis"[MeSH Terms] OR "leptospirosis"[All Fields] OR "leptospiroses"[All Fields] OR ("leptospira"[MeSH Terms] OR "leptospira"[All Fields] OR "leptospirae"[All Fields] OR "leptospiras"[All Fields])) AND ((((("acute"[All Fields] OR "acutely"[All Fields] OR "acutes"[All Fields]) AND ("kidney"[MeSH Terms] OR "kidney"[All Fields] OR "kidneys"[All Fields] OR "kidney s"[All Fields] OR ("renal"[All Fields] OR "renals"[All Fields]))) AND ("injurie"[All Fields] OR "injuried"[All Fields] OR "injuries"[MeSH Subheading] OR "injuries"[All Fields] OR "wounds and injuries"[MeSH Terms] OR ("wounds"[All Fields] AND "injuries"[All Fields]) OR "wounds and injuries"[All Fields] OR "injurious"[All Fields] OR "injury s"[All Fields] OR "injuryed"[All Fields] OR "injurys"[All Fields] OR "injury"[All Fields])) OR (("lung"[MeSH Terms] OR "lung"[All Fields] OR "pulmonary"[All Fields] OR ("lung"[MeSH Terms] OR "lung"[All Fields])) AND ("blood"[MeSH Subheading] OR "blood"[All Fields] OR "blood"[MeSH Terms] OR "bloods"[All Fields] OR "haematology"[All Fields] OR "hematology"[MeSH Terms] OR "hematology"[All Fields] OR "haematoma"[All Fields] OR "hematoma"[MeSH Terms] OR "hematoma"[All Fields] OR "haemorrhage"[All Fields] OR "hemorrhage"[MeSH Terms] OR "hemorrhage"[All Fields] OR "haemorrhages"[All Fields] OR "hemorrhages"[All Fields] OR "haemorrhagic"[All Fields] OR "haemorrhaging"[All Fields] OR "hematologies"[All Fields] OR "haematomas"[All Fields] OR "hematomas"[All Fields] OR "hematoma s"[All Fields] OR "hematomae"[All Fields] OR "hemorrhaged"[All Fields] OR "hemorrhagic"[All Fields] OR "hemorrhagical"[All Fields] OR "hemorrhaging"[All Fields]))) AND ("steroid*"[All Fields] OR "corticosteroid*"[All Fields] OR "glucocorticoid*"[All Fields] OR ("methylprednisolone"[MeSH Terms] OR "methylprednisolone"[All Fields] OR "methylprednisolon"[All Fields]) OR ("dexamethason"[All Fields] OR "dexamethasone"[MeSH Terms] OR "dexamethasone"[All Fields] OR "dexamethasone s"[All Fields] OR "dexamethasones"[All Fields]) OR ("prednisolon"[All Fields] OR "prednisolone"[MeSH Terms] OR "prednisolone"[All Fields]) OR ("prednison"[All Fields] OR "prednisone"[MeSH Terms] OR "prednisone"[All Fields]) OR ("cyclophosphamide"[MeSH Terms] OR "cyclophosphamide"[All Fields] OR "cyclophosphamid"[All Fields] OR "cyclophosphamide s"[All Fields] OR "cyclophosphamides"[All Fields]))	27
CENTRAL	(severe AND (leptospirosis OR leptospira)) AND ((acute (kidney OR renal) injury) OR ((pulmonary OR lung) hemorrhage)) AND ((steroid* OR corticosteroid* OR glucocorticoid* OR methylprednisolone OR dexamethasone OR prednisolone OR prednisone) OR cyclophosphamide)	2

PRISMA Flow Diagrams



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Included Studies

Characteristics of Included Studies

Author Year	Study design	Country (Period)	N	Population	Intervention Group(s)	Control Group	Outcomes
Alian 2014	Randomized double-blind clinical trial	Iran (2011 - 2013)	56	Patients with leptospirosis and moderate to severe thrombocytopenia	n=28 **Standard care +** **Prednisolone** 1 mg/kg/day for maximum 7 days	n=28 **Standard care + placebo** (1) antibiotic therapy with ceftriaxone 1 g IV daily	Pulmonary hemorrhage (hemoptysis and tachypnea); Renal involvement (azotemia and oliguria)

Quality Assessment of Included Studies

Quality assessment of included RCTs using RoB-2

Author Year	Study design	D1	D2	D3	D4	D5	Overall assessment	Remarks
Alian 2014	Randomized double-blind clinical trial	-	+	+	+	+	-	Applicable to outcomes pulmonary and renal involvement

Notes:

- D1 Risk of bias arising from randomization process
- D2 Risk of bias due to deviations from the intended interventions
- D3 Risk of bias due to missing outcome data
- D4 Risk of bias in measurement of the outcome
- D5 Risk of bias in selection of the reported result

Legend:

+	Low risk of bias
-	Some concerns
x	Serious risk of bias

GUIDELINE QUESTION 7: Should acellular pertussis vaccines be used instead of whole cell pertussis vaccines to prevent pertussis in infants?

Research Question: Among infants, how effective and safe are acellular pertussis vaccines compared to whole pertussis vaccines in preventing pertussis?	
Population	Infants
Intervention / Treatment	Acellular pertussis vaccine
Comparator	Whole cell pertussis vaccine
Outcomes	Incidence of pertussis in infants (up to one year of age); safety (any adverse events, serious adverse events)
Subgroups (if any)	Not applicable
Methods	RCTs; NRSIs including observational studies

Evidence Reviewers: Dr. Ma. Theresa M. Collante, Mr. Howell Henrian G. Bayona
Date of Last Search: November 10, 2024

Statement of the Evidence

Compared to whole cell pertussis vaccines, acellular pertussis vaccines result in little to no difference in efficacy in terms of prevention of pertussis in infants. However, acellular pertussis vaccines result in higher antibody levels against pertussis antigen/s compared to whole cell pertussis vaccines.

For adverse outcomes, acellular pertussis vaccines result in lower proportion of patients developing limpness, neurological disabilities, infantile spasms, encephalitis/encephalopathy, autism, speech disorders, and life-threatening reactions, and needing emergency department visits and hospitalizations,, but little to no difference in proportion of patients developing serious adverse events in general, including death, death alone, seizures, hypotonic-hyporesponsive episodes, sudden infant death syndrome, cerebellar ataxia, and generalized cyanosis.

Overall certainty for the effectiveness outcomes was downgraded to **moderate** due to imprecision, while overall certainty for adverse reactions was **low**.

Review Methods

A systematic search was done on 10 November 2024 using Medline, CENTRAL, EMBASE, and HERDIN Plus with a combined MeSH and free text search using the terms acellular pertussis vaccine, whole cell pertussis vaccine, and infants.

We included randomized controlled trials (RCT) that compared acellular pertussis vaccines against whole cell pertussis vaccines infants and observational studies for adverse events. Quality assessment was done using Cochrane Risk of Bias Tool 2 and ROBINS-I. Outcomes are confirmed cases of pertussis, immunogenicity, and

adverse reactions, including serious adverse events, neurological disorders, and other systemic and local reactions. No limits were used in terms of date of publication.

Recommendations from Other Groups

Most organizations, including the World Health Organization (WHO), Center for Disease Control and Prevention (CDC), Philippine Pediatric Society, Pediatric Infectious Disease Society of the Philippines, and Philippine Foundation for Vaccination, and American Academy of Pediatrics (AAP), **recommend a 3-dose primary DTP/DTaP series starting at 6 weeks or at 2, 4, and 6 month**s, with some variations in booster recommendations. While the WHO and Philippine guidelines have **no preference between acellular and whole-cell pertussis vaccines**, the CDC and AAP specifically recommend the acellular pertussis vaccine. Strength of recommendation and certainty of evidence were not specified in all the evaluated CPGs.

Group	Recommendation	Remarks
World Health Organization position[18] (weekly epidemiological record August 2015)	3-dose primary series at 2, 4, and 6 months as early as 6 weeks	No preference between acellular and whole cell pertussis vaccine.
Philippine Pediatric Society, Pediatric Infectious Disease Society of the Philippines, and Philippine Foundation for Vaccination Childhood Immunization Schedule[19] (2025)	DTP primary series of 3 doses 4 weeks apart	No preference between acellular and whole cell pertussis vaccine.
Center for Disease Control and Prevention Recommendations of the Advisory Committee on Immunization Practices 2019 report[20] (published in January 2020)	Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine Primary (3 doses) • 1 dose at ages 2, 4, and 6 mos	Acellular pertussis vaccine specifically recommended.
American Academy of Pediatrics[21] (2023)	Diphtheria, tetanus, and pertussis (DTaP) vaccination (minimum age: 6 weeks [4 years for Kinrix or Quadracel]) 5-dose series (3-dose primary series at age 2, 4, and 6 months, followed by booster doses at ages 15–18 months and 4–6 years)	Acellular pertussis vaccine specifically recommended.

Ongoing Studies and Research Gaps

No ongoing trials were found comparing acellular pertussis vaccines with whole cell pertussis vaccines in infants. However a phase 2b trial in the US was done one to assess the immunogenicity and safety of BPZE1, an intranasal live attenuated pertussis vaccine, compared with the tetanus–diphtheria–acellular pertussis vaccine (Tdap), which showed promising results.[22]

[18] WHO. Pertussis vaccines: WHO position paper, August 2015--Recommendations. Vaccine. 2016 Mar 14;34(12):1423-5. doi: 10.1016/j.vaccine.2015.10.136. Epub 2015 Nov 10. PMID: 26562318.
[19] Philippine Pediatric Society, Pediatric Infectious Disease Society of the Philippines, and Philippine Foundation for Vaccination. 2025. Childhood Immunization Schedule. https://www.pidsphil.org/home/.
[20] Havers FP, Moro PL, Hunter P, Hariri S, Bernstein H. Use of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccines: Updated Recommendations of the Advisory Committee on Immunization Practices - United States, 2019. MMWR Morb Mortal Wkly Rep. 2020 Jan 24;69(3):77-83. doi: 10.15585/mmwr.mm6903a5. PMID: 31971933; PMCID: PMC7367039.
[21] American Academy of Pediatrics. Whooping Cough (Pertussis): Symptoms, Treatment & Prevention. 2023. https://www.healthychildren.org/English/safety-prevention/immunizations/Pages/Your-Babys-First-Vaccines.aspx.
[22] Keech C, Miller VE, Rizzardi B, Hoyle C, Pryor MJ, Ferrand J, Solovay K, Thalen M, Noviello S, Goldstein P, Gorringe A, Cavell B, He Q, Barkoff AM, Rubin K, Locht C. Immunogenicity and safety of BPZE1, an intranasal live attenuated pertussis vaccine, versus tetanus-diphtheria-acellular pertussis vaccine: a randomised, double-blind, phase 2b trial. Lancet. 2023 Mar 11;401(10379):843-855. doi: 10.1016/S0140-6736(22)02644-7. PMID: 36906345.

Search Strategy

Database search strategy and yield (as of November 10, 2024)

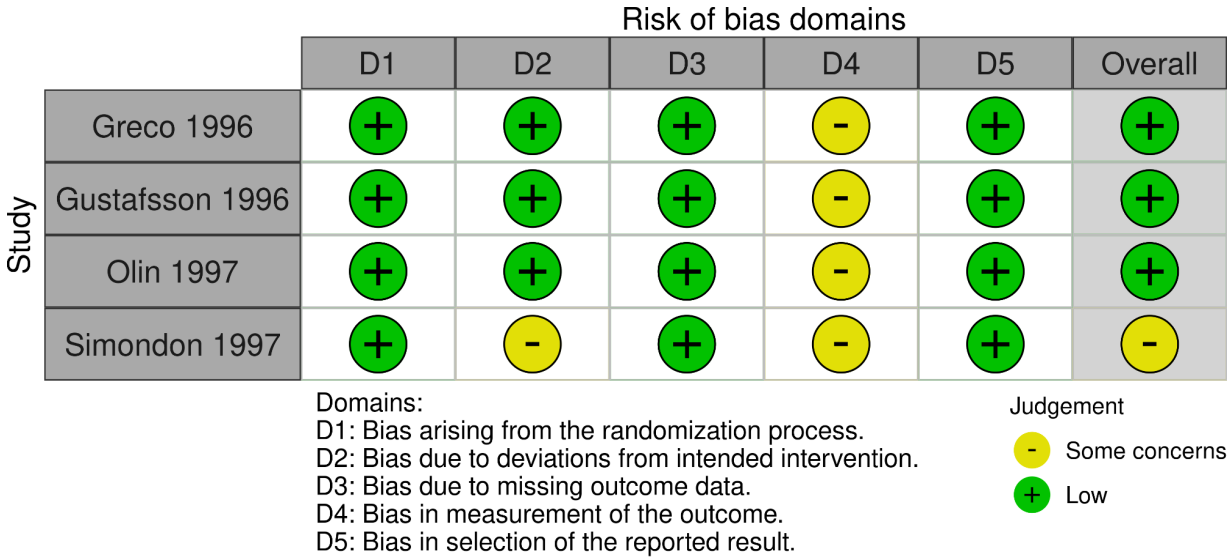
Database searched	Search strategy (syntax used for searching)	Initial yield	Screening results	Included
MEDLINE	(("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields] OR "infants"[All Fields]) AND (("acellular"[All Fields] OR "acellularity"[All Fields] OR "acellularization"[All Fields] OR "acellularized"[All Fields]) AND ("pertussis vaccine"[MeSH Terms] OR ("pertussis"[All Fields] AND "vaccine"[All Fields]) OR "pertussis vaccine"[All Fields])) AND (("whole"[All Fields] OR "wholeness"[All Fields] OR "wholes"[All Fields]) AND ("cells"[MeSH Terms] OR "cells"[All Fields] OR "cell"[All Fields]) AND ("pertussis vaccine"[MeSH Terms] OR ("pertussis"[All Fields] AND "vaccine"[All Fields]) OR "pertussis vaccine"[All Fields]))) AND ((excludepreprints[Filter]) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter]) AND (fft[Filter]) AND (humans[Filter]) AND (english[Filter]) AND (infant[Filter]))	95	32	4
CENTRAL	#1 Diphtheria-Tetanus-acellular Pertussis Vaccines #2 Pertussis vaccine #3 #1 OR #2 #4 infants #5 #3 AND #4 #6 Diphtheria-Tetanus-whole cell Pertussis Vaccines #7 #5 AND #6	52 (10 same as MEDLINE)	12	3
EMBASE	#1 infant:ab,ti #2 'pertussis vaccine':ab,ti #3 #1 AND #2 #4 #1 AND #2 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim)	40	13	0
HERDIN	Pertussis vaccine, filter: clinical trials	6	0	0

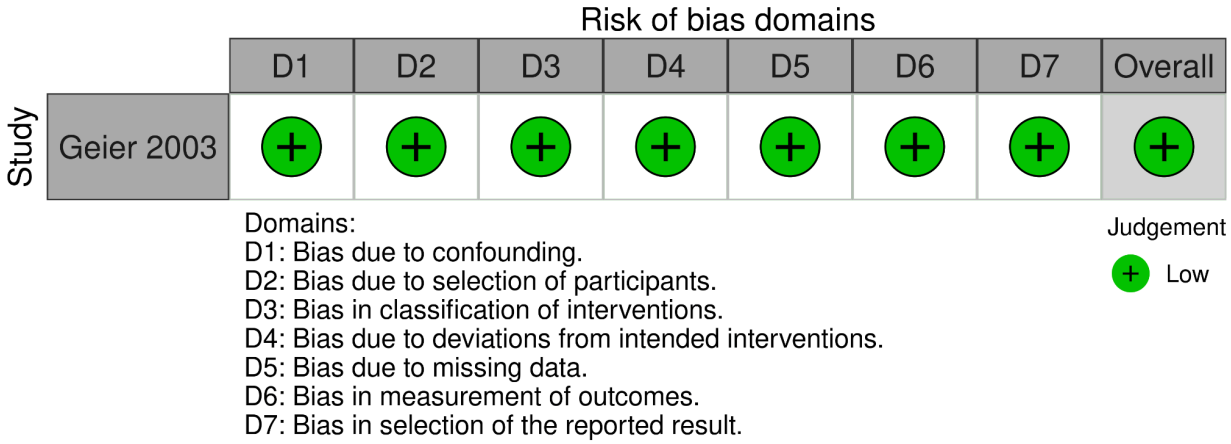
Included Studies

Characteristics of Included Studies

Study	Design	Population	Comparators	Outcome
Greco 1996 Progetto Pertosse working Working Group, Italy	Randomized controlled double-blind trial	n=14,571 infants in Italy 3 doses acellular pertussis vaccine (Smithkline n=4,481 and Biocine n=4,452) Given at 6-12, 13-20, and 21-28 weeks of age (with 4-12 weeks between doses) Followed up for an average of 17 months Booster dose DT at 6 months after 3rd dose	Whole-cell pertussis vaccine (n=4,348) or Biocide DT (n=1,470)	**Incidence of pertussis** (≥21 days of paroxysmal cough, with infection confirmed by culture or serologic testing, onset of cough at least 30 days from completion of immunization, note: vaccine efficacy also computed after 1st dose) **Immunogenicity** (Antibody levels - geometric mean) **Adverse events** (occurring on 8 consecutive evenings after each dose; local and systemic symptoms)
Olin 1997 Ad Hoc Group for the Study of Pertussis Vaccines, Italy	Randomized controlled double-blind trial	n=82,892 2-3 mo in Swedish countries 3 doses of acellular pertussis vaccines 2-component: n=20,697 3-component: n=20,728 5-component: n=20,747 Given at age 3, 5, and 12 months, or age 2, 4, and 6 months of age Followed up for an average of 22 months	UK whole-cell pertussis vaccine (n=20,720)	**Incidence of pertussis** (culture-confirmed *B pertussis* with at least 21 consecutive days of paroxysmal cough (typical pertussis), and culture-confirmed *B pertussis* with or without any cough (pertussis infection) after 2nd and 3rd doses **Immunogenicity** (Antibody levels - logarithmic) **Adverse events** (fever and seizures)
Simondon 1997	Randomized controlled double-blind trial	n=4,181 infants in Senegal 3 doses of 2-component acellular pertussis vaccine (n=1,847) Two weekly follow-ups post-vaccination Followed up to 6 to 12 months if with adverse reaction/s	Whole-cell pertussis vaccine (n=1,772)	**Incidence of pertussis** (21 days or more of paroxysmal cough, with infection confirmed by culture or serologic testing) **Adverse events** (Persistent crying, hypotonic-hyporesponsive episodes, and seizures)
Gustafsson 1996	Randomized controlled double-blind trial	n=9,829 infants in Stockholm 3 doses of acellular pertussis vaccine 2-component (n=2,566) 5-component (n=2,587) Followed for about 2 years	Whole-cell pertussis vaccine (n=2,102) Or DT (n=2,574)	**Incidence of pertussis** (21 days or more of paroxysmal cough, with infection confirmed by culture or serologic testing) **Immunogenicity** (Antibody levels - logarithmic) **Adverse events** (general symptoms and local reactions)

Quality Assessment of Included Studies



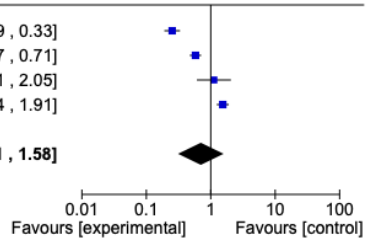


Forest Plots

Confirmed pertussis

Study or Subgroup	Acellular pertussis vaccine Events	Total	Whole cell pertussis vaccine Events	Total	Weight	Risk ratio IV, Random, 95% CI
Greco 1996	73	8933	141	4348	25.5%	0.25 [0.19 , 0.33]
Gustafsson 1996	218	5085	148	2001	25.8%	0.58 [0.47 , 0.71]
Olin 1997	34	35365	15	17453	22.9%	1.12 [0.61 , 2.05]
Simondon 1997	197	1847	123	1772	25.8%	1.54 [1.24 , 1.91]
Total (Wald[a])		**51230**		**25574**	**100.0%**	**0.70 [0.31 , 1.58]**
Total events:	522		427			

Test for overall effect: Z = 0.85 (P = 0.39)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 0.66; Chi² = 107.74, df = 3 (P < 0.00001); I² = 97%

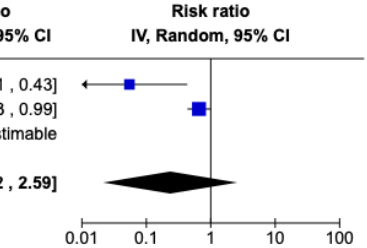


Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

Adverse events: hypotonic-hyporesponsive episodes

Study or Subgroup	Acellular pertussis vaccine Events	Total	Whole cell pertussis vaccine Events	Total	Weight	Risk ratio IV, Random, 95% CI
Greco 1996	1	27474	9	13520	41.4%	0.05 [0.01 , 0.43]
Olin 1997	67	61368	34	20457	58.6%	0.66 [0.43 , 0.99]
Simondon 1997	0	6881	0	6595		Not estimable
Total (Wald[a])		**95723**		**40572**	**100.0%**	**0.23 [0.02 , 2.59]**
Total events:	68		43			

Test for overall effect: Z = 1.18 (P = 0.24)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 2.51; Chi² = 5.35, df = 1 (P = 0.02); I² = 81%

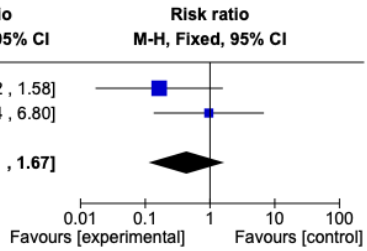


Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

Adverse events: seizures

Study or Subgroup	Acellular pertussis vaccine Events	Total	Whole cell pertussis vaccine Events	Total	Weight	Risk ratio M-H, Fixed, 95% CI
Greco 1996	1	27474	3	13520	66.3%	0.16 [0.02 , 1.58]
Simondon 1997	2	6881	2	6595	33.7%	0.96 [0.14 , 6.80]
Total		**34355**		**20115**	**100.0%**	**0.43 [0.11 , 1.67]**
Total events:	3		5			

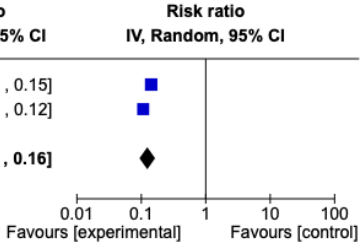
Test for overall effect: Z = 1.22 (P = 0.22)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 1.34, df = 1 (P = 0.25); I² = 25%



Adverse events: fever ≥ 38°C

Study or Subgroup	Acellular pertussis vaccine Events	Total	Whole cell pertussis vaccine Events	Total	Weight	Risk ratio IV, Random, 95% CI
Greco 1996	1567	27474	5425	13520	51.2%	0.14 [0.13 , 0.15]
Gustafsson 1996	379	4905	1447	2001	48.8%	0.11 [0.10 , 0.12]
Total (Wald[a])		**32379**		**15521**	**100.0%**	**0.12 [0.09 , 0.16]**
Total events:	1946		6872			

Test for overall effect: Z = 14.65 (P < 0.00001)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.04; Chi² = 24.40, df = 1 (P < 0.00001); I² = 96%

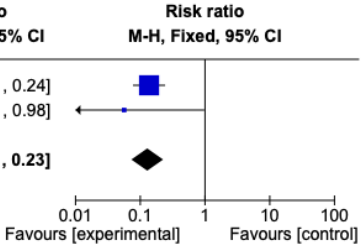


Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Adverse events: persistent crying ≥ 3 hrs

Study or Subgroup	Acellular pertussis vaccine Events	Total	Whole cell pertussis vaccine Events	Total	Weight	Risk ratio M-H, Fixed, 95% CI
Greco 1996	15	27474	54	13520	89.3%	0.14 [0.08 , 0.24]
Simondon 1997	0	6881	8	6595	10.7%	0.06 [0.00 , 0.98]
Total		**34355**		**20115**	**100.0%**	**0.13 [0.07 , 0.23]**
Total events:	15		62			

Test for overall effect: Z = 7.13 (P < 0.00001)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.37, df = 1 (P = 0.54); I² = 0%



GUIDELINE QUESTION 8: Should reverse transcription polymerase chain reaction (RT-PCR) or multiplex rapid antigen test (RAT) be used to confirm the diagnosis of avian influenza in suspected patients?

Research Question: Among patients suspected with avian influenza, how accurate and safe are multiplex rapid antigen tests and RT-PCR?	
Population	Patients suspected with avian influenza
Intervention / Treatment	Multiplex rapid antigen test/lateral flow immunoassay; RT-PCR
Comparator	Viral isolation (as comparison for multiplex and RT-PCR); RT-PCR (as comparison for multiplex RAT)
Outcomes	Diagnostic accuracy measures (sensitivity, specificity, false positive rates, false negative rates, etc.); cost-effectiveness; improved clinical outcomes improved clinical outcomes
Subgroups (if any)	By timing of testing
Methods	Observational studies (diagnostic cross-sectional, cohort); diagnostic RCTs

Evidence Reviewers: Dr Timothy Hudson David C. Carandang, Mr. Kerwyn Jim C. Chan, Mr. Howell Henrian G. Bayona
Date of Last Search: November 19, 2024; updated May 18, 2025

Statement of the Evidence

Multiplex RAT
One case-control study showed that multiplex RAT may have poor sensitivity compared to RT-PCR, but the evidence is very uncertain. Many people who actually have avian influenza may have a false negative result on RAT.

RT-PCR
Two studies compared RT-PCR with viral isolation, but did not report diagnostic accuracy measures. RT-PCR was noted to have lower per-patient cost than viral culture, though no studies evaluated cost-effectiveness. The overall certainty of the evidence is very low.

Review Methods

A systematic search was done from October 1, 2024 until November 29, 2024 using Medline, Embase, CENTRAL, HERDIN Plus, and Global Index Medicus (composed of IMSEAR, IMEMR, WPRO, AIM, and LILACS) with a combined MeSH and free text search using the terms avian influenza, RT-PCR, and multiplex rapid antigen test.

Only observational studies (diagnostic cross-sectional, cohort) and diagnostic randomized controlled trials that either compared the accuracy of multiplex RAT and RT-PCR with viral isolation or multiple RAT with RT-PCR in

diagnosing avian influenza in humans were included. Outcomes of interest included diagnostic accuracy measures (sensitivity, specificity, false positive rates, false negative rates, etc.), cost-effectiveness, and improved clinical outcomes.

The methodological quality of each study was appraised using the Quality Assessment of Diagnostic Accuracy Studies - version 2 (QUADAS-2). Studies with similar PICO/PIRT were pooled and the effect estimates were determined using the "mada" and "meta" packages of R statistical software version 4.3.3.

Recommendations from Other Groups

Various health agencies emphasize the importance of accurate laboratory testing for avian influenza. The World Health Organization (WHO) **does not recommend the general use of rapid diagnostic tests** for detecting human A(H5N1) infections due to limited reliability. The Centers for Disease Control and Prevention (CDC) recommends rRT-PCR testing for suspected novel influenza A virus cases. Similarly, the European CDC identifies RT-PCR as the gold standard, while also acknowledging the role of antigen testing, virus isolation, sequencing, and serology. The Ministry of Health Malaysia defines a confirmed A/H5 case based on positive results from PCR, viral culture, immunofluorescence, or serological testing, such as a fourfold rise in antibodies.

Group or Agency	Recommendation
World Health Organization[23] (accessed May 9, 2025, updated January 2007)	The use of commercially available rapid diagnostic tests for the detection of human A(H5N1) infections is in general not recommended.
Centers for Disease Control and Prevention[24] (accessed May 9, 2025, updated September 12, 2024)	Therefore, influenza A testing by rRT-PCR is recommended at public health laboratories and CDC for any patient with suspected novel influenza A virus infection.
European Centers for Disease Control and Prevention[25] (accessed May 9, 2025, updated September 12, 2024)	The gold standard for detection and identification of AIV from respiratory samples is RT-PCR, but laboratory testing can also involve antigen testing, virus isolation, sequencing and/or serological testing.
Ministry of Health Malaysia, Communicable Disease Surveillance Section, Disease Control Division[26] (accessed May 9, 2025, updated Sept 2004)	defines a confirmed influenza A/H5 case as an individual for whom laboratory testing demonstrates one or more of the following: a. positive viral culture for Influenza A/H5; b. **positive PCR for Influenza A/H5**; c. immunofluorescence antibody (IFA) test positive using Influenza A/H5 monoclonal antibodies; d. 4-fold rise in Influenza A/H5 specific antibody titre in paired serum samples.

NOTE: The strength of recommendation and certainty of evidence were not specified in any of the guidelines listed above.

Ongoing Studies and Research Gaps

No study comparing multiplex RAT directly with viral isolation was found (as of May 9, 2025). More studies comparing multiplex RAT with RT-PCR and RT-PCR with viral isolation are needed for more robust recommendations.

[23] World Health Organization. (2007). WHO guidelines for investigation of human cases of avian influenza A (H5N1), [Rev.]. World Health Organization. https://iris.who.int/handle/10665/69416

[24] CDC. Interim Guidance on Testing and Specimen Collection for Patients with Suspected Infection with Novel Influenza A Viruses with the Potential to Cause Severe Disease in Humans. September 12, 2024 [accessed 09 May 2025]; Available from: https://www.cdc.gov/bird-flu/php/severe-potential/index.html

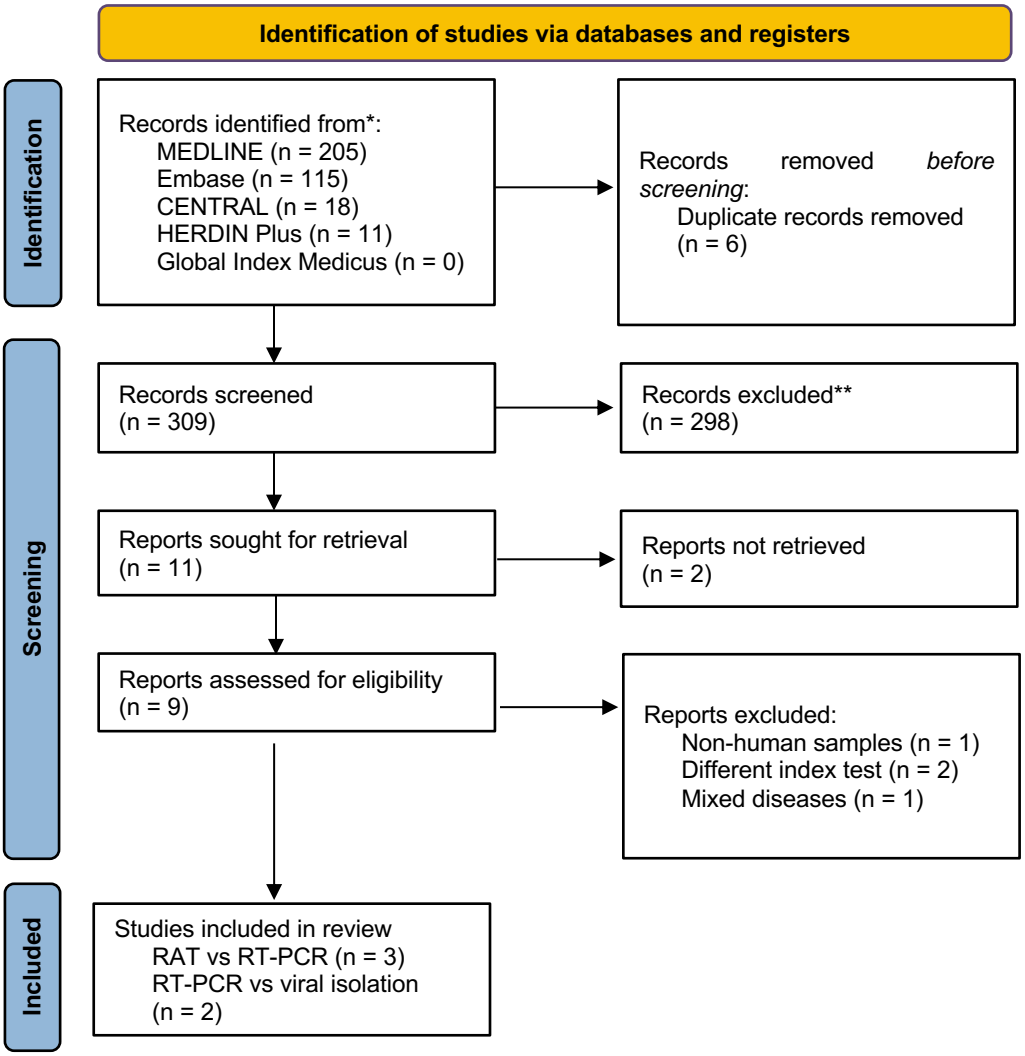
[25] European Centre for Disease Prevention and Control. Investigation protocol for human exposures and cases of avian influenza in the EU/EEA. Stockholm: ECDC; 2023.

[26] Ministry of Health Malaysia. Alert, Enhanced Surveillance and Management of Avian Influenza in Human. September 2004

Search Strategy

Database	Search Strategy / Search Terms	Date and Time of Search	Results	
			Yield	Potentially Eligible
MEDLINE	"Influenza in Birds/diagnosis"[Mesh] AND (((RT-PCR OR Reverse Transcriptase Polymerase Chain Reaction OR Reverse Transcriptase PCR) OR (rapid antigen test OR RAT OR multiplex RAT OR multiplex rapid antigen test OR (multiplex lateral flow AND (test OR device)) OR multiplex rapid antigen detection test OR multiplex rapid test)))	11/13/24, 4:00 pm	201	1
		updated 05/17/25, 7:30 am	+4	0
Embase	#1 'avian influenza'/exp OR 'avian influenza' #2 'reverse transcription polymerase chain reaction' #3 'rt pcr' OR 'real-time pcr':ti,ab #4 'rapid antigen test' #5 'multiplex':ti,ab #6 #4 OR #5 OR #3 OR #2 #7 #1 AND #6 #8 sensitivity OR specificity OR diagnosis OR accuracy OR 'false positive' OR 'false negative' OR 'detection rate' OR 'receiver operat*':ti,ab,kw #9 #7 AND #8 #10 #9 NOT 'nonhuman'/de #11 #9 NOT 'nonhuman'/de AND ([embase]/lim OR [preprint]/lim)	05/17/25, 7:36 am	115	8
CENTRAL	#1 avian influenza #2 RT-PCR OR Reverse Transcriptase Polymerase Chain Reaction OR Reverse Transcriptase PCR #3 rapid antigen test OR RAT OR multiplex RAT OR multiplex rapid antigen test #4 #2 or #3 #5 #4 and #1	05/17/25, 7:40 am	18	0
HERDIN Plus	avian influenza	05/17/25, 7:42 am	11	0
IMSEAR	"Influenza in Birds/diagnosis"[Mesh] AND (((RT-PCR OR Reverse Transcriptase Polymerase Chain Reaction OR Reverse Transcriptase PCR) OR (rapid antigen test OR RAT OR multiplex RAT OR multiplex rapid antigen test OR (multiplex lateral flow AND (test OR device)) OR multiplex rapid antigen detection test OR multiplex rapid test)))	05/18/25, 3:51 am	0	0
IMEMR	"Influenza in Birds/diagnosis"[Mesh] AND (((RT-PCR OR Reverse Transcriptase Polymerase Chain Reaction OR Reverse Transcriptase PCR) OR (rapid antigen test OR RAT OR multiplex RAT OR multiplex rapid antigen test OR (multiplex lateral flow AND (test OR device)) OR multiplex rapid antigen detection test OR multiplex rapid test)))	05/18/25, 3:52 am	0	0
WPRO	"Influenza in Birds/diagnosis"[Mesh] AND (((RT-PCR OR Reverse Transcriptase Polymerase Chain Reaction OR Reverse Transcriptase PCR) OR (rapid antigen test OR RAT OR multiplex RAT OR multiplex rapid antigen test OR (multiplex lateral flow AND (test OR device)) OR multiplex rapid antigen detection test OR multiplex rapid test)))	05/18/25, 3:52 am	0	0
AIM	"Influenza in Birds/diagnosis"[Mesh] AND (((RT-PCR OR Reverse Transcriptase Polymerase Chain Reaction OR Reverse Transcriptase PCR) OR (rapid antigen test OR RAT OR multiplex RAT OR multiplex rapid antigen test OR (multiplex lateral flow AND (test OR device)) OR multiplex rapid antigen detection test OR multiplex rapid test)))	05/18/25, 3:53 am	0	0
LILACS	"Influenza in Birds/diagnosis"[Mesh] AND (((RT-PCR OR Reverse Transcriptase Polymerase Chain Reaction OR Reverse Transcriptase PCR) OR (rapid antigen test OR RAT OR multiplex RAT OR multiplex rapid antigen test OR (multiplex lateral flow AND (test OR device)) OR multiplex rapid antigen detection test OR multiplex rapid test)))	05/18/25, 3:53 am	0	0

PRISMA Flow Diagram

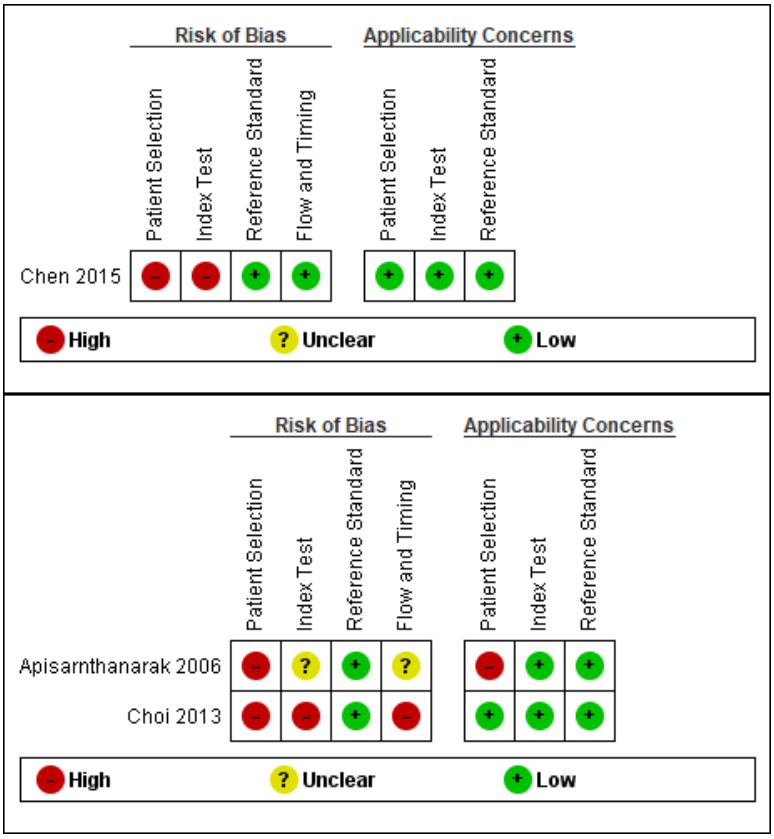


Included Studies

Characteristics of Included Studies

Author	Design	Population (n)	Sample type	Index test/s	Reference standard	Findings
Rapid antigen tests						
Chen et al 2015 (EMBASE)	Case-control	110 throat swab or sputum specimens from 53 A(H7N9)-infected patients 115 A(H3N2) and 97 A(H1N1)pdm09 throat swab specimens	throat swab or sputum	Wondfo Flu A test, colloidal gold method Wondfo H7 Subtype test, colloidal gold method	real-time RT-PCR	The usefulness of currently available seasonal influenza RDTs for diagnosing A(H7N9) virus infections is limited because of their low sensitivity for detecting virus in upper respiratory tract specimens.
RT-PCR						
Apisarnthanarak et al 2006 (EMBASE)	Cohort	115 clinically suspected patients	Tracheal aspirate	RT-PCR Serologic testing	Viral culture	8 (7%) patients with influenza A (H3N2) were identified; none had H5N1. Estimated costs for RT-PCR per sample is $25 while for culture, $30.
Choi et al 2013 (MEDLINE)	Case-control	319 specimens tested retrospectively (159 were influenza virus culture positive (seasonal 19 A/H1, 47 A/H3, 63 A/H1pdm09 and 30 B viruses) and 160 were culture negative)	Throat swab	Multiplex Real-time RT-PCR	Viral culture	Analytical positive predictive value (PPV), negative predictive value (NPV) sensitivity and specificity were 100%, 94.1%, 93.7% and 100%, respectively.

Quality Assessment of Included Studies



Forest Plot

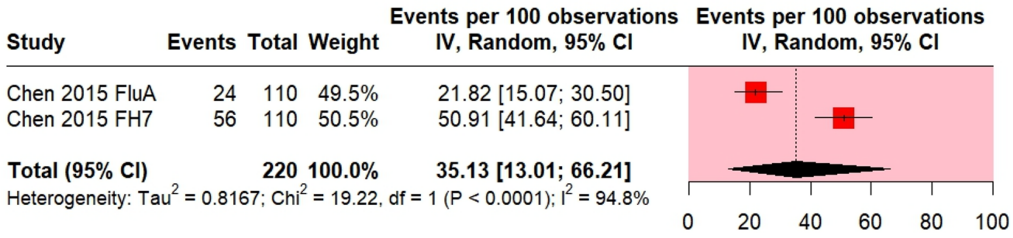


Table 2. RDT positivity rates for detection of different influenza A virus subtypes in real-time reverse transcription PCR–positive specimens*

	Wantai Flu A Dot-ELISA†			Wondfo Flu A test, colloidal gold method†			Wondfo H7 Subtype test, colloidal gold method		
C_t	H7N9	H1N1 pdm09	H3N2	H7N9	H1N1 pdm09	H3N2	H7N9	H1N1 pdm09	H3N2
<25	7/7 (100)	12/14 (86)	22/24 (92)	7/7 (100)	12/14 (86)	22/24 (92)	7/7 (100)	0/14 (0)	0/24 (0)
25–30	18/38 (47)	35/54 (65)	35/55 (64)	11/38 (29)	23/54 (43)	23/55 (42)	28/38 (74)	0/54 (0)	0/55 (0)
>30	13/65 (20)	8/29 (28)	15/36 (42)	6/65 (9)	7/29 (24)	15/36 (42)	21/65 (32)	0/29 (0)	0/36 (0)
Total	38/110 (35)	55/97 (57)	72/115 (63)	24/110 (22)	42/97 (43)	60/115 (52)	56/110 (51)	0/97 (0)	0/115 (0)

*Values are no. specimens positive by RDT/no. specimens positive by real-time reverse transcription PCR (%). C_t, cycle threshold; RDT, rapid diagnostic test.
†Sensitivity for influenza A (H7N9) virus was significantly lower than that for either H1N1 pdm09 or influenza A (H3N2) viruses ($p<0.01$, χ^2 test), but no statistically significant difference in sensitivity was found between A(H1N1)pdm09 and influenza A (H3N2) viruses.

GUIDELINE QUESTION 9: Should quarantine be recommended for close contacts of confirmed or suspected cases of mpox?

Research Question: Among close contacts of confirmed or suspected mpox, how effective is quarantine in reducing the incidence of mpox?	
Population	Close contacts of confirmed mpox cases, close contacts of suspected mpox cases
Intervention / Treatment	Quarantine (include different duration of quarantine)
Comparator	No quarantine
Outcomes	Incidence of mpox
Subgroups (if any)	Not applicable
Methods	Observational studies

Evidence Reviewers: Dr. Lester Lloyd Vinz Ngo, Mr. Kerwyn Jim C. Chan, Mr. Howell Henrian G. Bayona
Date of Last Search: November 10, 2024

Statement of the Evidence

Based on very low certainty evidence from 2 observational studies, quarantine may result in lower mpox incidence but this effect is very uncertain and with unknown harms. Mathematical modeling studies also suggest that quarantine probably may be effective in reducing mpox transmission, though their impact varies by setting, adherence, presence of vaccination, duration of quarantine, and resource constraints.

The certainty of evidence is **very low**.

Review Methods

A systematic search was done last search November 10, 2024 using MEDLINE via Pubmed, Embase, Cochrane Library and Central, with a combined MeSH and free text search using the terms monkeypox, mpox, suspected monkeypox, confirmed monkeypox, quarantine, infectivity, isolation, cordon, lockdown, community containment, containment area and incubation period. We also searched for ongoing studies in the NIH *clinicaltrials.gov* and WHO ICTRP. Preprints were also searched using medrxiv, and preprints.org. No limits were placed on age, and duration of quarantine.

We aimed to include observational study designs that reported on the outcomes of any quarantine intervention on the reduction in mpox incidence or mpox-related deaths. Quarantine was defined as physical separation and restriction of movement of individuals exposed to confirmed or suspected cases of mpox, which excludes travel-related measures or environmental measures applied to exposed individuals. As observational studies regarding this topic were expected to be limited, we also included modeling studies as indirect evidence on the benefits and risks of quarantine for mpox close contacts. Observational or modeling studies reporting on the duration of infectivity and mpox incubation period were also included to provide indirect evidence to support an optimal duration of quarantine.

For observational studies, ROBINS-I V2 was used to assess the risk of bias (ROB).[27] As no validated ROB tool currently exists specifically for mathematical transmission models, we followed the best practice recommendations of the International Society for Pharmacoeconomics and Outcomes (ISPOR) for dynamic mathematical transmission model.[28] Dynamic transmission models are capable of estimating the direct and indirect effects that may arise from an infectious disease and changes of risk over time. We chose these three criteria: 1. Whether the model was dynamic; 2. Whether the study authors conducted uncertainty analyses on key model parameters and assumptions; 3. Whether the results provided estimates of the change in the burden of infection due to the intervention, because they exhibit sound methodological decisions that have the largest impact on the outcomes. For modelling studies fulfilling all three criteria we had 'no concerns to minor concerns' regarding their quality; if one or more categories were unclear (e.g. because of incomplete reporting) we had 'moderate concerns'; if one or more categories were not fulfilled, we had 'major concerns'.

The certainty of evidence on the net effects of quarantine was rated using GRADE. Findings of the review were summarized using the GRADEPro tool to create an evidence profile. Due to the heterogeneity and nature of the included studies, we synthesized the results narratively and in tabular form.

Recommendations from Other Groups

Currently available CPGs from WHO, India, Malaysia as well as the PSMID suggest isolation among individuals with mpox but <u>not</u> among close contacts of mpox. It is only recommended to monitor symptoms for close contacts of confirmed and suspected cases of mpox. None of the reviewed CPGs had specified strength of recommendation or corresponding certainty of evidence ratings.

Group or Agency	Recommendation	
	For infected patients with mpox	**Close contacts of mpox**
Guidance of the management of mpox (Philippine Society of Microbiology and Infectious Diseases - version 1, as of September 8, 2024)	**Infected patients** should isolate themselves from others **until all the lesions have crusted over, the scabs have fallen off and a new layer of skin has formed underneath. This can take up to 3 to 4 weeks.**	*<u>No mention of close contacts exposed to mpox cases</u>* **Asymptomatic HCP** with exposures to infected patients do not need to be excluded from work, but should have daily **self-monitoring for signs and symptoms of infection for 21 days after their last exposure.**
Ayush guideline for management of Monkeypox (Ministry of Ayush - Government of India)*Date published unavailable	*<u>No mention of isolation among infected patients and close contacts exposed to mpox cases</u>* The **incubation period** (interval from infection to onset of symptoms) of mpox is usually from 6 to 13 days but can range from 5 to 21 days.	
Guidelines for management of monkeypox (Ministry of Health and Welfare - Government of India, as of August, 2024)	**For infected cases**, isolation continues until **all lesions have resolved and scabs have completely fallen off.**	**Contacts** should be **monitored at least daily for the onset of signs/symptoms for a period of 21 days** from the last contact with a patient or their contaminated materials during the infectious period. In case of occurrence of fever clinical/lab evaluation is warranted. Health workers who have unprotected exposure to patients with mpox or possibly contaminated materials **do not need to be excluded from work**

[27] Sterne, J. A., Hernán, M. A., Reeves, B. C., Savović, J., Berkman, N. D., Viswanathan, M., Henry, D., Altman, D. G., Ansari, M. T., Boutron, I., Carpenter, J. R., Chan, A. W., Churchill, R., Deeks, J. J., Hróbjartsson, A., Kirkham, J., Jüni, P., Loke, Y. K., Pigott, T. D., Ramsay, C. R., … Higgins, J. P. (2016). ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ (Clinical research ed.), 355, i4919. https://doi.org/10.1136/bmj.i4919

[28] Pitman, R., Fisman, D., Zaric, G. S., Postma, M., Kretzschmar, M., Edmunds, J., Brisson, M., & ISPOR-SMDM Modeling Good Research Practices Task Force (2012). Dynamic transmission modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--5. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research, 15(6), 828–834. https://doi.org/10.1016/j.jval.2012.06.011

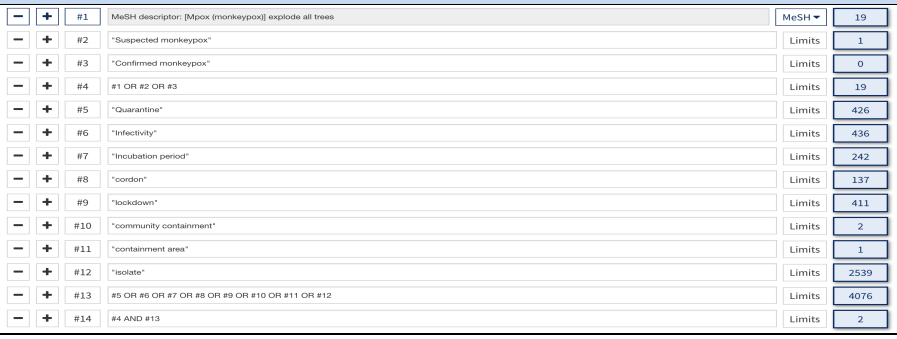
Group or Agency	Recommendation	
	For infected patients with mpox	Close contacts of mpox
		duty if asymptomatic, but should undergo active surveillance for symptoms for 21 days.
Guidelines on monkeypox management in Malaysia (Ministry of Health - as of January 18, 2023)	**A mpox case** is ordered to undergo isolation under section 14 of Prevention and Control of Infectious Disease Act 1988 [Act 342] in a quarantine station i.e. hospital.	**Contacts with high risk of infections** need **to be observed for 21 days from the date of last exposure** to the confirmed case, for any mpox symptoms and signs.
Clinical management and infection prevention and control of monkeypox (WHO - as of June 2022)	**Patients with mpox** who are cared for at home should remain in isolation and refrain from close contact **until their skin lesions have crusted, the scabs have fallen off and a fresh layer of skin has formed underneath**	*No mention of civilian contacts exposed to mpox cases* **Health workers** who have had an occupational exposure (ie not wearing appropriate PPE) do not need to be excluded from work if they are asymptomatic, but should u**ndergo active surveillance for symptoms for 21 days post-exposure**; and be instructed not to work with vulnerable patients
Infection prevention and control and water, sanitation and hygiene measures for home care and isolation for mpox in resource-limited settings (WHO - Oct 2024)	The **person with mpox** should remain in a **separate, well ventilated area (i.e. a separate room or area separated with a curtain or screen) and away from other household members, pets and shared areas of the home** unless that person needs to do urgent or essential activities, such as obtaining care at a facility or getting exercise or fresh air	Household members should be **monitored, or should self-monitor, daily for the onset of signs or symptoms of an mpox infection for a period of 21 days from the last day they had contact with the person who had probable or confirmed mpox** or **with their potentially contaminated materials (or up to two days before the onset of** symptoms, if feasible and appropriate) In a household, the **21-day period would begin once the person with mpox no longer requires isolation.**
Surveillance, case investigation and contact tracing for mpox (monkeypox): interim guidance, (WHO - 20 March 2024)	**No recommendation.**	Contacts of probable and confirmed cases **should be monitored, or should self-monitor, daily for any sign or symptom for a period of 21 days** from last contact with an infectious case or potentially contaminated materials.
Mpox Monitoring and Risk Assessment for People Exposed in the Community (CDC - April 11, 2025)	**No recommendation.**	Anyone with an **exposure to people or animals with mpox** should **monitor their health for signs or symptoms consistent with mpox for 21 days after their last exposure.** **No recommendation of quarantine for exposed persons who remain asymptomatic**

Ongoing Studies and Research Gaps

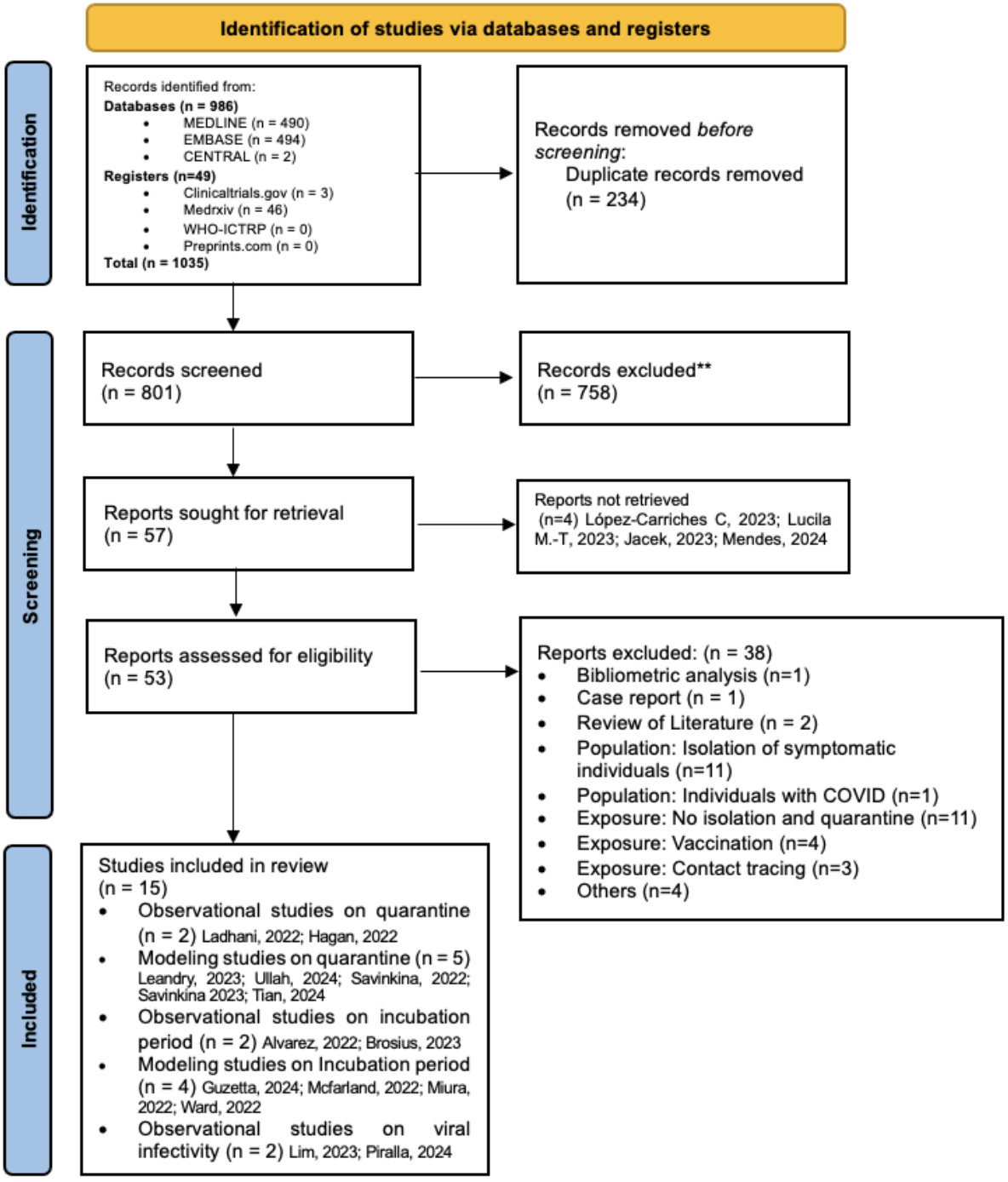
Current evidence focuses primarily on vaccination, treatment, and isolation of active mpox cases, with limited data on quarantine of close contacts. No ongoing studies addressing quarantine effects were identified in trial registries or preprint databases. High-quality observational or interventional studies are needed to assess the effectiveness, duration, cost-effectiveness, acceptability, and feasibility of quarantine for exposed individuals.

Search Strategy

Date base searched	Search strategy (Syntax)	Initial yield
MEDLINE	("mpox monkeypox"[MeSH Terms] OR ("mpox"[All Fields] AND "monkeypox"[All Fields]) OR "mpox monkeypox"[All Fields] OR "monkeypox"[All Fields] OR "suspected monkeypox"[All Fields] OR "confirmed monkeypox"[All Fields]) AND ("Quarantine"[All Fields] OR "Infectivity"[All Fields] OR "isolation"[All Fields] OR "cordon"[All Fields] OR "lockdown"[All Fields] OR "community containment"[All Fields] OR "Containment area"[All Fields] OR "incubation period"[All Fields])	490

Date base searched	Search strategy (Syntax)	Initial yield
CENTRAL		2
EMBASE	#12 #11 AND #3 #11 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 #10 'incubation time':ti,ab #9 cordon*:ti,ab #8 'containment area':ti,ab #7 'community containment':ti,ab #6 lockdown:ti,ab #5 isolat*:ti,ab #4 quarantin*:ti,ab #3 #1 OR #2 #2 mpox:ti,ab #1 'monkeypox'/exp OR 'monkeypox'	494
clinicaltrials.gov	("monkeypox" OR "Suspected monkeypox" OR "confirmed monkeypox") AND ("quarantine" OR "isolate" OR "cordon" OR "lockdown" OR "community containment" OR "containment area")	3
WHO ICTRP	“Monkeypox” AND ("quarantine" OR "isolate" OR "cordon" OR "lockdown" OR "community containment" OR "containment area") *Manually reviewed 17 trials objectives and outcomes (both primary and secondary) – No trials can be included	0
Medrxiv	("monkeypox" OR "Suspected monkeypox" OR "confirmed monkeypox") AND ("quarantine" OR "isolate" OR "cordon" OR "lockdown" OR "community containment" OR "containment area")	46
Preprints.org	“Monkeypox” AND ("quarantine" OR "isolate" OR "cordon" OR "lockdown" OR "community containment" OR "containment area") – No articles found	0

PRISMA Flow Diagram



Included and Excluded Studies

Studies on Quarantine: Observational Studies

No.	Study ID	Study design	Setting	Population	Intervention	Outcome	Results
1	Ladhani 2022	Observational study (outbreak investigation or contact tracing analysis)	England (educational settings, from May to July 2022)	N=440 100 staff and 340 students who were contacts of confirmed mpox cases in educational settings **Exposure type:** All exposures classified as Category 2 (medium risk) - contact w/in 1 meter with mpox case for ≥ 15 min or sharing a car Subgroups: 1. n≥154 children (11-16 y.o) in secondary school 2. n≥100 adult staff in secondary school 3. n=38 children (5–11 y.o.) in primary school 4. n=6 adult staff in primary school 5. n=58 children (2-3 y.o.) in nursery 6. n=4 adult staff in nursery 7.n=90 children (4-5 y.o.) in reception year 8. n=10 adults staff/parents in reception year	**Isolation at home** Excluded from school for 21 days without the need for self- isolation at home in the first three exposures settings (secondary school, primary, nursery) **Isolation into bubbles** For those in the reception year; separated from other unexposed children in the final exposure setting (reception year) **Vaccination (MVA-BN)** 186 children aged 2–11 years were offered one dose of MVA-BN vaccine and 21 (11%) were vacci- nated, mostly between 7 and 14 days after exposure	**Incidence of mpox** (ffup: 28 days; confirmed with positive RT-PCR at a reference laboratory)	**0 cases identified** among 340 exposed students and 100 staff after last exposure to the index cases in any of the 4 education settings)
2	Hagan 2022	Observational study (case investigation)	Chicago, Illinois (County Jail, from July-August 2022)	N=57 Residents of the County Jail potentially exposed to an mpox case (median age 38 [21-63 yrs]; 100% males; 53% Black, 30% White, 14% Latino, 4% Asian). Low knowledge on mpox symptoms and transmission. **Exposure type:** All classified as intermediate-risk (i.e., w/in 6 ft of patient for cumulative period ≥ 3 hrs w/o wearing mask, or had contact with skin or clothing and skin lesions or body fluids or materials). Exposure occurred within 7 days between the patient's symptom onset and his isolation.	**Quarantine** (no further details given) **Post-exposure prophylaxis** (MVA-BN vaccine [JYNNEOS] for 7-14 days after last exposure; accepted only by 13 (23%) of residents)	**Incidence of mpox** (ffup: day 15 and 22 with serologic testing with anti-*Orthopoxvirus* IgM and IgG)	36/57 (63.2%) of residents remained in detention 14/57 (24.5%) consented to IgM testing. **None of the specimens tested positive for IgM.**

Studies on Quarantine: Modeling Studies

No.	Study ID (Country)	Aims	Type of model	Model assumptions	Interventions	Results
1	Leandry 2023 (Tanzania)	To investigate the dynamics mpox virus spread in humans and rodents, with quarantine and vaccination interventions	**Deterministic dynamic mathematical model** (based on a system of ordinary differential equations that describe the flow of individuals between different compartments within each population)	Susceptible humans (S_H) exposed (E_H) quarantined (Q_H) infectious (I_H) recovered (R_H) vaccinated (V_H)	**Quarantine** (unspecified number of days or other implementation details) **Vaccination**	**Effective reproductive number (virus transmission)** Implementing quarantine measures significantly reduces the human infected population compared to a scenario where no intervention is taken. As the quarantine rate is increased, the reproductive number decreases. However, the study does not provide a single numerical value quantifying this reduction in a direct comparison between a scenario with a specific quarantine rate and one with no quarantine
2	Ullah 2024 (Bangladesh)	To comprehensively examine the effects of non-pharmaceutical interventions on disease control	**Deterministic mathematical model** (based on a system of ordinary differential equations to describe the dynamics of mpox in human and animal populations) **Fractional-order derivative approach** (to incorporate the memory effect in the epidemic's dynamics) **Evolutionary game theory (EGT) framework** (integrated in the model to account for how human behavior to participate or not in a quarantine)	Compartmental model for humans (S, E, I, Q, R) and animals (S, E, I, R) Various transmission routes Protection rates, incubation periods, and recovery rates are defined Quarantine decisions based on cost and information	**Quarantine or self-isolation** period (δ) of 14 to 28 days. After this, individuals return to the susceptible pool. Isolation characteristics are not specified separately.	**Number of infected, quarantined, recovered individuals, basic reproduction number (R0), final epidemic size (FES), average social payoff (ASP), and the impact of various parameters on these outcomes** If exposed and infected people flawlessly maintain the quarantine or self-isolation rules and regulations, then mpox disease would be under control and finally fade out without showing any devastating scenarios Quarantine policies significantly slow epidemic transmission, making them pivotal in combating mpox Higher quarantine costs deter people from complying with quarantine measures, leading to an uptick in disease cases due to inadequate treatment and vaccination Strict adherence to quarantine policies emerges as a critical factor in mpox control
3	Savinkina 2023 (USA; College campus)	To estimate the likelihood of an mpox outbreak and the potential impact of mitigation measures in a residential college setting.	**Stochastic dynamic SEIR model** (to simulate and predict the spread of infectious diseases by accounting for both the disease process and random variability in transmission over time)	Hypothetical cohort of 6500 students, divided into high-risk group (men having sex with men, 10%) and low-risk group Planning horizon of 100 days	**Isolation, quarantine, and vaccination of close contacts** (14 days; symptomatic students are detected and	Similarly, **quarantine was not shown to reduce likelihood of outbreak**, but did reduce average number of cases per outbreak when R0,H was 2.4 Without mitigation, there was an 83% likelihood of sustained transmission, leading to an average of 183 cases over 100 days. With 20%, 50%, and 80% isolation, average infections fell to 117, 37, and 8, respectively.

No.	Study ID (Country)	Aims	Type of model	Model assumptions	Interventions	Results
				Base case starting from one symptomatic infection introduced into the high-risk group External introductions (1 additional per 100-day period) of mpox from the broader community, assumed to occur exclusively in members of the high-risk group Transmission is assumed to be frequency- dependent Casual contact between all students Additional transmission exclusively between high-risk students representing potential sexual transmission. Basic Reproductive Number (R0) of 2.4 for the high-risk group (R0,H) and 0.8 for the low-risk group and casual contact (R0,L)	removed from the infectious population; detection and isolation rates of 0%, 20%, 50%, and 80% of cases were explored. **Vaccination** Reactive vaccination of contacts of detected cases and pre-emptive vaccination of a proportion of the high-risk group (50%)	Reactive vaccination of close contacts could also reduce outbreak likelihood and size. The authors note limitations, including that the model is a stylized portrayal and simplifies mixing patterns (not a network model), which may affect estimates of the high-risk group's influence. They also mention being limited by the data available to parameterize the model due to the novelty of the 2022 outbreak, particularly concerning R0 estimates and epidemiology assumptions, addressing this via sensitivity analyses.
4	Tian 2024 (China)	To evaluate the effectiveness of two sets of border screening strategies considering China's border entry and quarantine policies	**Probabilistic model** (to estimate importation risk based on international travel data) **Mathematical model** (to simulate the effectiveness of border screening strategies and quaratine) **Analytical solution** (based on existing epidemiological theory to estimate the local outbreak probability) **Generalized linear model** (to assess the contribution of air travel	International travelers entering Chinese mainland, especially for those who had travel history to regions with an on-going mpox epidemic within 21 days of border entry Travel-related mpox cases mainly come from major cities Infected individuals could travel internationally during their 9 day incubation period 6.5 day delay between symptom onset and reporting Probability of international air travel based on 2019-2022 data	**Mandatory quarantine** (Scenario 1; transferred to hospital for 7-21 day medical observation, PCR test) **Self-isolation / optional quarantine** (Scenario 2; those reporting epidemiological link to mpox case undergo medical observation, avoid sexual	**Risk of mpox importation** Reduced international air travel and stringent border entry policies significantly decreased mpox importations during the peri-pandemic period (2022) compared to a hypothetical pre-pandemic scenario (2019) **Detection of mpox (effectiveness of border screening)** Existing mandatory quarantine policy (Scenario 1) with a quarantine duration of 10 days could detect over 80% of imported mpox infections, regardless of self-reporting rates. Detection rate of mpox increases with the quarantine duration **Local outbreak probability** If even a single undetected mpox case was introduced into the active MSM population with low immunity, there was a considerable risk (around 42% with R0=1.8

No.	Study ID (Country)	Aims	Type of model	Model assumptions	Interventions	Results
			and MSM population size to local outbreaks)	Sexual contact network among men who have sex with men (MSM) in China is heterogeneous	activity, self-isolate and test upon showing symptoms	and k=0.88) of triggering local transmission, and this risk increased to over 95% with six or more undetected cases. Emergency vaccination could reduce this probability **Contribution of air travel and MSM population** A positive correlation between the number of reported mpox cases at the provincial level and both air-travel volume and the size of the active MSM population, especially their interaction.

Studies on Incubation

Author	Type of study	Setting	Population	Outcome	Results
Alvarez 2022	Cross-sectional epidemiologic study	Colombia	11 RT-PCR confirmed cases of mpox in Pereira, Colombia	Incubation period	Mean incubation period = **7.1 days (95% CI 4.9–9.9)** 5th–95th percentiles 1.9–15.0 days. Adjusted mean incubation period using the Weibull parametric distribution from likely exposure to onset. Results for gamma and log-normal distributions were similar.
Brosius 2023	Cohort	Belgium	25 high-risk contacts of 23 cases in Belgium	Period of seroconversion of mpox	Among 5/6 (83.3%) definitely infected cases with typical presentation, viral DNA was detected **1 to 4 days** before the onset of any symptoms
Guzetta 2022	Modelling	Italy	Cases testing positive by MPX specific PCR (n = 15 persons with known date of exposure and 15 persons with known travel dates in Canary Islands)	Incubation period; generation time (difference between the date of infection of a confirmed case and those of secondary cases); reproduction time	Mean incubation period = **9.1 days (95% CI 6.5–10.9)** Mean generation time = **12.5 days (95% CI 7.5–17.3)** Reproduction number among men who have sex with men = **2.43 (95% CI 1.82–3.26)**
Mcfarland 2022	Modelling (double censored models)	Berlin	Individuals who attended a fetish festival in Antwerp, Belgium, a gay pride festival in Gran Canaria, Spain or a particular club in Berlin, Germany	Incubation Period	Median incubation period: **8–9 days** 5th-95th percentiles: **2–3 to 20–23 days** Half of cases were between 4 and 11 days Longer incubation periods (>21 days in ~5%) are important for public health monitoring recommendations.
Miura 2022	Modelling (likelihood based approach)	Netherlands	Individuals with exposure to confirmed mpox (18 cases)	The duration of the incubation period	Mean incubation period: **8.5 days (95% CrI 6.6–10.9)** 5th-95th percentile of **4.2–17.3 days**. The reported incubation intervals for monkeypox were best described by a lognormal distribution.
Ward 2022	Modelling (Time delay distribution)	UK	54 individuals from UK contact tracing with symptom onset and probable exposure dates	Incubation period, mean serial interval (time from symptom onset in a primary case to	Mean incubation period: **7.6 days (95% CrI 6.5–9.9)** (ICC model) **7.8 days (95% CrI 6.6–9.2)** (ICRTC model)

Author	Type of study	Setting	Population	Outcome	Results
			between 6 May and 1 August 2022; PCR confirmed mpox	symptom onset in a secondary case)	Mean serial interval: **8.0 days (95% CrI 6.5 to 9.8)** (ICC model) **9.5 days (7.4 to 12.3)** (ICRTC model) Specific to the UK outbreak demographic (primarily MSM) and clade. Shorter median serial interval compared to incubation suggests considerable pre-symptomatic transmission. Isolation period based on 95th centile (16 to 23 days) is adequate

Studies on Viral Infectivity

Author	Type of study	Setting	Population	Outcome	Results
Lim 2023	Correlational	Australia	Patients with positive mpox PCR	Viral detection	Viral loads in **skin lesions were significantly higher than those in throat or nasopharyngeal samples** (median Ct 22.0 vs 29.0, p = 0.0013 and median Ct 22.0 vs 36.5, p = 0.0001, respectively). Similarly, **viral loads were significantly higher in anal samples compared to throat or nasopharyngeal samples** (median Ct 20.0 vs. 29.0, p=<0.0001 and median Ct 20.0 vs. 36.5, p=<0.0001, respectively).
Piralla 2024	Cohort	Italy	Patients with positive mpox PCR	Viral detection	MPXV DNA detection was **more frequent in the skin (94.4%) with the longest median time of viral clearance (16 days).**

List of Excluded Studies

No.	Title/Author, Trial Registration	Reasons for Exclusion
Bibliometric analysis (n=1)		
1	Bibliometric analysis of human monkeypox research from 1975 to 2022 and novel prevention and control strategies **Lin, 2022** Lin J, Li G, Zhong P, Zeng Q, Liu L, Chen L. Bibliometric analysis of human monkeypox research from 1975 to 2022 and novel prevention and control strategies. Front Public Health. 2022 Sep 27;10:995965. doi: 10.3389/fpubh.2022.995965. PMID: 36238247; PMCID: PMC9550883.	Bibliometric analysis of number of published articles
Case report (n=1)		
2	Imported monkeypox, Singapore **Yong, 2020** Yong SEF, Ng OT, Ho ZJM, Mak TM, Marimuthu K, Vasoo S, Yeo TW, Ng YK, Cui L, Ferdous Z, Chia PY, Aw BJW, Manauis CM, Low CKK, Chan G, Peh X, Lim PL, Chow LPA, Chan M, Lee VJM, Lin RTP, Heng MKD, Leo YS. Imported Monkeypox, Singapore. Emerg Infect Dis. 2020 Aug;26(8):1826-1830. doi: 10.3201/eid2608.191387. Epub 2020 Apr 27. PMID: 32338590; PMCID: PMC7392406.	Case report
Review of Literature (n = 2)		
3	Monkeypox virus (MPXV) Vandenbergen L., Vandercam G., Hoornaert E., Sluijters A., Yombi J.C. (2022), Monkeypox virus (MPXV). Louvain Medical: **Internal medicine and infectious diseases**.	Review of Literature

No.	Title/Author, Trial Registration	Reasons for Exclusion
4	Monkeypox: A Review **Singhal, 2022** Singhal, T., Kabra, S. K., & Lodha, R. (2022). Monkeypox: A Review. *Indian journal of pediatrics*, *89*(10), 955–960. https://doi.org/10.1007/s12098-022-04348-0	Review of Literature
Population: Isolation of symptomatic individuals (n=11)		
5	Keep Calm and Carry On: Projected Case Burden and Duration of the 2022 Monkeypox Outbreak in Non-endemic Countries **Bisanzioo, 2022** Bisanzio D, Reithinger R. Projected burden and duration of the 2022 Monkeypox outbreaks in non-endemic countries. Lancet Microbe. 2022 Sep;3(9):e643. doi: 10.1016/S2666-5247(22)00183-5. Epub 2022 Jun 23. PMID: 35753315; PMCID: PMC9225111.	The population was individuals already with mpox
6	Transmission dynamics of Monkeypox virus: a mathematical modelling approach. **Peter, 2022** Peter, O. J., Kumar, S., Kumari, N., Oguntolu, F. A., Oshinubi, K., & Musa, R. (2022). Transmission dynamics of Monkeypox virus: a mathematical modelling approach. *Modeling earth systems and environment*, *8*(3), 3423–3434. https://doi.org/10.1007/s40808-021-01313-2	The population was individuals already with mpox
7	Modelling the effectiveness of an isolation strategy for managing mpox outbreaks with variable infectiousness profiles **Jeong, 2024** Jeong, Y. D., Hart, W. S., Thompson, R. N., Ishikane, M., Nishiyama, T., Park, H., Iwamoto, N., Sakurai, A., Suzuki, M., Aihara, K., Watashi, K., Op de Coul, E., Ohmagari, N., Wallinga, J., Iwami, S., & Miura, F. (2024). Modelling the effectiveness of an isolation strategy for managing mpox outbreaks with variable infectiousness profiles. *Nature communications*, *15*(1), 7112. https://doi.org/10.1038/s41467-024-51143-w	The population was individuals already with mpox
8	Modelling the impact of timelines of testing and isolation on disease control **Li, 2024** Li, A., Wang, Z., & Moghadas, S. M. (2023). Modelling the impact of timelines of testing and isolation on disease control. *Infectious Disease Modelling*, *8*(1), 58–71. https://doi.org/10.1016/j.idm.2022.11.008	The population was individuals already with mpox
9	New numerical dynamics of the fractional monkeypox virus model transmission pertaining to nonsingular kernels **Qurashi, 2023** Qurashi, M. A., Rashid, S., Alshehri, A. M., Jarad, F., & Safdar, F. (2023). New numerical dynamics of the fractional monkeypox virus model transmission pertaining to nonsingular kernels. *Mathematical biosciences and engineering : MBE*, *20*(1), 402–436. https://doi.org/10.3934/mbe.2023019	The population was individuals already with mpox
10	Quantifying the impact of individual and collective compliance with infection control measures for ethical public health policy **Roberts, 2023** Roberts, D., Jamrozik, E., Heriot, G. S., Slim, A. C., Selgelid, M. J., & Miller, J. C. (2023). Quantifying the impact of individual and collective compliance with infection control measures for ethical public health policy. *Science advances*, *9*(18), eabn7153. https://doi.org/10.1126/sciadv.abn7153	The population was individuals already with mpox
11	Study and prediction of the 2022 global monkeypox epidemic. **Wei, 2022**	The population was individuals already with mpox

No.	Title/Author, Trial Registration	Reasons for Exclusion
	Wei, F., Peng, Z., Jin, Z., Wang, J., Xu, X., Zhang, X., Xu, J., Ren, Z., Bai, Y., Wang, X., Lu, B., Wang, Z., Xu, J., & Huang, S. (2022). Study and prediction of the 2022 global monkeypox epidemic. *Journal of biosafety and biosecurity*, *4*(2), 158–162. https://doi.org/10.1016/j.jobb.2022.12.001	
12	Modeling vaccination and control strategies for outbreaks of monkeypox at gatherings **Yuan, 2022** Yuan P, Tan Y, Yang L, Aruffo E, Ogden NH, Bélair J, Arino J, Heffernan J, Watmough J, Carabin H, Zhu H. Modeling vaccination and control strategies for outbreaks of monkeypox at gatherings. Front Public Health. 2022 Nov 25;10:1026489. doi: 10.3389/fpubh.2022.1026489. PMID: 36504958; PMCID: PMC9732364.	The population was individuals already with mpox
13	An effectiveness study of vaccination and quarantine combination strategies for containing mpox transmission on simulated college campuses **Huang, 2024** Huang, Q., Sun, Y., Jia, M., Jiang, M., Xu, Y., Feng, L., & Yang, W. (2024). An effectiveness study of vaccination and quarantine combination strategies for containing mpox transmission on simulated college campuses. *Infectious Disease Modelling*, *9*(3), 805–815. https://doi.org/10.1016/j.idm.2024.04.004	The population was individuals already with mpox
14	Border control strategies for reducing importation risk of Clade Ib Mpox **Shihui, 2024** Shihui Jin, Tong Guan, Akira Endo, Gregory Gan, A. Janhavi, Gang Hu, Keisuke Ejima, Jue Tao Lim, Borame L Dickens. (2024) Border control strategies for reducing importation risk of Clade Ib Mpox. medRxiv 2024.09.10.24313380; doi: https://doi.org/10.1101/2024.09.10.24313380	The population was individuals already with mpox
15	The expected economic burden on the healthcare system because of quarantining patients with monkeypox virus **Alshahrani, 2023** Alshahrani A. The expected economic burden on the healthcare system because of quarantining patients with monkeypox virus. Saudi Med J. 2023 Mar;44(3):231-236. doi: 10.15537/smj.2023.44.3.20220515. PMID: 36940962; PMCID: PMC10043895.	The population was individuals already with mpox
Population: Individuals with COVID (n=1)		
16	Modeling approaches to inform travel-related policies for COVID-19 containment: A scoping review and future directions **Koiso, 2024** Koiso, S., Gulbas, E., Dike, L., Mulroy, N. M., Ciaranello, A. L., Freedberg, K. A., Jalali, M. S., Walker, A. T., Ryan, E. T., LaRocque, R. C., & Hyle, E. P. (2024). Modeling approaches to inform travel-related policies for COVID-19 containment: A scoping review and future directions. *Travel medicine and infectious disease*, *62*, 102730. https://doi.org/10.1016/j.tmaid.2024.102730	Only discuss about COVID
Exposure: No isolation and quarantine (n=11)		
17	Differential Diagnosis, Prevention Measures, and Therapeutic Interventions for Enhanced Monkeypox (Mpox) Care. **Khan, 2024** Khan, I., S, M., Dixit, T., Shinkre, R., Ravindran, S., & Bandyopadhyay, S. (2024). Differential Diagnosis, Prevention Measures, and Therapeutic Interventions for Enhanced Monkeypox (Mpox) Care. *Cureus*, *16*(5), e60724. https://doi.org/10.7759/cureus.60724	No isolation and quarantine studies
18	Insights into the emergence and evolution of monkeypox virus: Historical perspectives, epidemiology, genetic diversity, transmission, and preventative measures. **Kurrey, 2024**	No isolation and quarantine studies

No.	Title/Author, Trial Registration	Reasons for Exclusion
	Krishna, S., Kurrey, C., Yadav, M., Mahilkar, S., Sonkar, S. C., Vishvakarma, N. K., Sonkar, A., Chandra, L., & Koner, B. C. (2024). Insights into the emergence and evolution of monkeypox virus: Historical perspectives, epidemiology, genetic diversity, transmission, and preventative measures. *Infectious medicine*, *3*(2), 100105. https://doi.org/10.1016/j.imj.2024.100105	
19	Management of patients with monkeypox virus infection and contacts in the community and in healthcare settings: a French position paper **Lepelletier, 2022** Lepelletier, D., Pozzetto, B., Chauvin, F., Chidiac, C., & High Council for Public Health national working groups (2022). Management of patients with monkeypox virus infection and contacts in the community and in healthcare settings: a French position paper. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*, *28*(12), 1572–1577. https://doi.org/10.1016/j.cmi.2022.08.018	No isolation and quarantine studies
20	Recent Outbreak of Monkeypox: Implications for Public Health Recommendations and Crisis Management in India. **Kumar, 2023** Kumar A, Borkar SK, Choudhari SG, Mendhe HG, Bankar NJ. Recent Outbreak of Monkeypox: Implications for Public Health Recommendations and Crisis Management in India. Cureus. 2023 Sep 21;15(9):e45671. doi: 10.7759/cureus.45671. PMID: 37868437; PMCID: PMC10589906.	No isolation and quarantine studies
21	Disease History, Pathogenesis, Diagnostics, and Therapeutics for Human Monkeypox Disease: A Comprehensive Review **Saied, 2022** Saied, A. A., Dhawan, M., Metwally, A. A., Fahrni, M. L., Choudhary, P., & Choudhary, O. P. (2022). Disease History, Pathogenesis, Diagnostics, and Therapeutics for Human Monkeypox Disease: A Comprehensive Review. *Vaccines*, *10*(12), 2091. https://doi.org/10.3390/vaccines10122091	No isolation and quarantine studies
22	Emerging infectious diseases, focus on infection prevention, environmental survival and germicide susceptibility: SARS-CoV-2, Mpox, and Candida auris **Weber, 2023** Weber, D. J., Rutala, W. A., & Sickbert-Bennett, E. (2023). Emerging infectious diseases, focus on infection prevention, environmental survival and germicide susceptibility: SARS-CoV-2, Mpox, and Candida auris. *American journal of infection control*, *51*(11S), A22–A34. https://doi.org/10.1016/j.ajic.2023.02.006	No isolation and quarantine studies
23	Enhancing Nursing Care in Monkeypox (Mpox) Patients: Differential Diagnoses, Prevention Measures, and Therapeutic Interventions. **Dubey, 2023** Dubey, T., Chakole, S., Agrawal, S., Gupta, A., Munjewar, P. K., Sharma, R., & Yelne, S. (2023). Enhancing Nursing Care in Monkeypox (Mpox) Patients: Differential Diagnoses, Prevention Measures, and Therapeutic Interventions. *Cureus*, *15*(9), e44687. https://doi.org/10.7759/cureus.44687	No isolation and quarantine studies
24	Epidemiology, Clinical Features, Diagnosis and Management of Monkeypox Virus: A Clinical Review Article. **Ghazanfar, 2022** Ghazanfar A. Epidemiology, Clinical Features, Diagnosis and Management of Monkeypox Virus: A Clinical Review Article. Cureus. 2022 Aug 30;14(8):e28598. doi: 10.7759/cureus.28598. PMID: 36185896; PMCID: PMC9521816.	No isolation and quarantine studies
25	Monkeypox 2022 Identify-Isolate-Inform: A 3I Tool for frontline clinicians for a zoonosis with escalating human community transmission. **Koenig, 2022** Koenig, K. L., Beÿ, C. K., & Marty, A. M. (2022). Monkeypox 2022 Identify-Isolate-Inform: A 3I Tool for frontline clinicians for a zoonosis with escalating human community transmission. *One health (Amsterdam, Netherlands)*, *15*, 100410. https://doi.org/10.1016/j.onehlt.2022.100410	No isolation and quarantine studies

No.	Title/Author, Trial Registration	Reasons for Exclusion
26	Monkeypox in humans: a new outbreak **Martin-Delgado, 2022** Martín-Delgado MC, Martín Sánchez FJ, Martínez-Sellés M, Molero García JM, Moreno Guillén S, Rodríguez-Artalejo FJ, Ruiz-Galiana J, Cantón R, De Lucas Ramos P, García-Botella A, García-Lledó A, Hernández-Sampelayo T, Gómez-Pavón J, González Del Castillo J, Muñoz P, Valerio M, Catalán P, Burillo A, Cobo A, Alcamí A, Bouza E. Monkeypox in humans: a new outbreak. Rev Esp Quimioter. 2022 Dec;35(6):509-518. doi: 10.37201/req/059.2022. Epub 2022 Jul 6. PMID: 35785957; PMCID: PMC9728594.	No isolation and quarantine studies
27	Evaluation of three control strategies to limit mpox outbreaks in an agent based model **Brainard, 2024** Brainard, Julii & Lake, Iain & Hunter, Paul. (2024). Evaluation of three control strategies to limit mpox outbreaks in an agent based model. 10.1101/2024.02.06.24302176.	Strategies only involves: Limit new sex partners, take up any offers for smallpox vaccination, and self-isolate
Exposure: Vaccination (n=4)		
28	Human monkeypox infection threat: A comprehensive overview **Kang, 2023** Kang, Y., Yu, Y., & Xu, S. (2023). Human monkeypox infection threat: A comprehensive overview. *PLoS neglected tropical diseases*, *17*(4), e0011246. https://doi.org/10.1371/journal.pntd.0011246	only vaccine was discussed
29	Current Insights into Diagnosis, Prevention Strategies, Treatment, Therapeutic Targets, and Challenges of Monkeypox (Mpox) Infections in Human Populations. **Patel, 2023** Patel, M., Adnan, M., Aldarhami, A., Bazaid, A. S., Saeedi, N. H., Alkayyal, A. A., Saleh, F. M., Awadh, I. B., Saeed, A., & Alshaghdali, K. (2023). Current Insights into Diagnosis, Prevention Strategies, Treatment, Therapeutic Targets, and Challenges of Monkeypox (Mpox) Infections in Human Populations. *Life (Basel, Switzerland)*, *13*(1), 249. https://doi.org/10.3390/life13010249	Prevention strategies only included vaccination, surveillance and detection
30	Factors potentially contributing to the decline of the mpox outbreak in the Netherlands, 2022 and 2023 **Haverkate, 2024** Haverkate, M. R., Willemstein, I. J., van Ewijk, C. E., Adam, P. C., Lanooij, S. J., Jonker-Jorna, P., van Bokhoven, C., van Rijckevorsel, G. G., Hoornenborg, E., David, S., Mollema, L., Te Wierik, M. J., Lange, J., Franz, E., de Melker, H. E., Op de Coul, E. L., & Hahné, S. J. (2024). Factors potentially contributing to the decline of the mpox outbreak in the Netherlands, 2022 and 2023. *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin*, *29*(21), 2300608. https://doi.org/10.2807/1560-7917.ES.2024.29.21.2300608	Vaccine effectiveness and behavior change was the only discussed topics
31	Monkeypox (Mpox) requires continued surveillance, vaccines, therapeutics and mitigating strategies **Roper, 2023** Roper, R. L., Garzino-Demo, A., Del Rio, C., Bréchot, C., Gallo, R., Hall, W., Esparza, J., Reitz, M., Schinazi, R. F., Parrington, M., Tartaglia, J., Koopmans, M., Osorio, J., Nitsche, A., Huan, T. B., LeDuc, J., Gessain, A., Weaver, S., Mahalingam, S., Abimiku, A., … McFadden, G. (2023). Monkeypox (Mpox) requires continued surveillance, vaccines, therapeutics and mitigating strategies. *Vaccine*, *41*(20), 3171–3177. https://doi.org/10.1016/j.vaccine.2023.04.010	Vaccine effectiveness was the only discussed topics
Exposure: Contact tracing (n=3)		
32	Impact of interventions on mpox transmission during the 2022 outbreak in Canada: a mathematical modeling study of three different cities **Oke, 2023**	The intervention was contact tracing

No.	Title/Author, Trial Registration	Reasons for Exclusion
	Oke, Idisi & Yusuf, Tunde & Adeniyi, Ebenezer & Onifade, Akindele & Oyebo, Yakub & Samuel, Akinyemi & Kareem, Lateef. (2023). Impact of Awareness Campaign on the Outbreak of Mpox: Mathematical Modelling Approach. 10.2139/ssrn.4530972.	No intervention of quarantine
33	Modelling the potential spread of Clade Ib MPXV in an Asia Pacific city **Jin, 2024** Jin, Shihui & Gan, Gregory & Endo, Akira & Prem, Kiesha & Tan, Rayner Kay Jin & Lim, Jue & Ejima, Keisuke & Dickens, Borame. (2024). Modelling the potential spread of Clade Ib MPXV in Asian cities. 10.1101/2024.10.16.24315640.	The intervention was contact tracing No intervention of quarantine
34	Assessing transmission risks and control strategy for monkeypox as an emerging zoonosis in a metropolitan area **Yuan, 2023** Yuan, P., Tan, Y., Yang, L., Aruffo, E., Ogden, N. H., Bélair, J., Heffernan, J., Arino, J., Watmough, J., Carabin, H., & Zhu, H. (2023). Assessing transmission risks and control strategy for monkeypox as an emerging zoonosis in a metropolitan area. *Journal of medical virology*, *95*(1), e28137. https://doi.org/10.1002/jmv.28137	The intervention was contact tracing No intervention of quarantine
Others (n=4)		
35	School-based interventions on Mpox: A scoping review **Amat, 2023** Amzat J, Kanmodi KK, Aminu K, Egbedina EA. School-based interventions on Mpox: A scoping review. Health Sci Rep. 2023 Jun 12;6(6):e1334. doi: 10.1002/hsr2.1334. PMID: 37313531; PMCID: PMC10259520.	It has only 1 study included; Plan to get the study included: Very low risk of mpox among staff and students after exposure to a confirmed case in educational settings, England, May to July 2022
36	Epidemiology-based analysis of the risks and elimination strategies of the monkeypox outbreak in 2022 **Chen, 2022** Chen, J. M., Chen, R. X., Gong, H. Y., Zhao, M. M., Ji, Y. F., Sun, M. H., Li, G. H., Tan, S. M., Zhang, G. H., & Chen, J. W. (2022). Epidemiology-based analysis of the risks and elimination strategies of the monkeypox outbreak in 2022. *Frontiers in veterinary science*, *9*, 1064766. https://doi.org/10.3389/fvets.2022.1064766	Only a showed a list of different strategies to prevent mpox outbreak
37	Infection prevention and control measures to reduce the transmission of mpox: a systematic review **Kuehn, 2024** Kuehn, R., Fox, T., Guyatt, G., Lutje, V., & Gould, S. (2024). Infection prevention and control measures to reduce the transmission of mpox: A systematic review. *PLOS global public health*, *4*(1), e0002731. https://doi.org/10.1371/journal.pgph.0002731	No studies identified that directly informed the research question; data from route of transmission frequency resulting in mpox infection was inferred.
38	Extended Human-to-Human transmission during a Monkeypox Outbreak in the Democratic Republic of the Congo **Nolen, 2016** Nolen LD, Osadebe L, Katomba J, Likofata J, Mukadi D, Monroe B, Doty J, Hughes CM, Kabamba J, Malekani J, Bomponda PL, Lokota JI, Balilo MP, Likafi T, Lushima RS, Ilunga BK, Nkawa F, Pukuta E, Karhemere S, Tamfum JJ, Nguete B, Wemakoy EO, McCollum AM, Reynolds MG. Extended Human-to-Human Transmission during a Monkeypox Outbreak in the Democratic Republic of the Congo. Emerg Infect Dis. 2016 Jun;22(6):1014-21. doi: 10.3201/eid2206.150579. Erratum in: Emerg Infect Dis. 2016 Oct;22(10). doi: 10.3201/eid2210.C22210. PMID: 27191380; PMCID: PMC4880088.	Different outbreak of mpox

Quality Assessment of Included Studies

Observational Studies

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias
Ladhani 2024	Moderate[a]	Low	Low	Moderate[b]	Low	Low	Low	Moderate
Hagan 2024	Moderate	Low	High[c]	Low	High[d]	High[e]	Low	High

[a]Confounding may have also been present since exposures were limited to category 2 (medium risk) -> means risk of getting infected is not really that high in these settings

[b]Some bias due to deviations from intended interventions (administration of co-intervention [vaccines] for some participants).

[c]High ROB also due to ascertainment of exposure since reporting of skin-to-skin or sexual contact might not have been reliable. Sharing utensils, linens also could not be reliably assessed.

[d]High ROB for missing data since only 36/57 (62.2%) of the initially exposed participants remained in the detention facility. And only 14/36 (39%) agreed to be tested for mpox serology (so in total 43/57 (75%) had unknown results)

[e]High ROB also for measurement since they used IgG only instead of more sensitive / gold standard diagnostics (RT-PCR)

Modeling Studies

Author and Year	Was the model a dynamic* (transmission) model?	Did the authors conduct uncertainty analyses** on the key assumptions that may have had an impact of the conclusions?	Do the results provide estimates of the change in the burden of infection due to the intervention?	Quality***
Leandry, 2023	Yes	Yes	Yes	No concerns to minor concerns
Ulllah, 2024	Yes	Unclear	Yes	Moderate concerns
Savinkina, 2023	Yes	Yes	Yes	No concerns to minor concerns
Tian, 2024	No	Unclear	Yes	Major concerns

GUIDELINE QUESTION 10: Should mpox vaccine be given to persons at risk?

Research Question: Among individuals who are at risk for mpox, how effective and safe is mpox vaccine?	
Population	At risk individuals (healthcare workers, immunocompromised patients, immunocompetent men having sex with men (MSM) individuals, pregnant and children)
Intervention / Treatment	Pre-exposure and post-exposure mpox vaccine
Comparator	No mpox vaccine
Outcomes	Efficacy outcomes; safety outcomes; cost-effectiveness
Subgroups (if any)	Persons at-risk for mpox infection; persons at-risk for severe disease
Methods	RCTs; observational studies

Evidence Reviewers: Dr. Nikko Theodore V. Raymundo, Mr. Howell Henrian G. Bayona
Date of Last Search: January 16, 2025

Statement of the Evidence

Among high risk individuals, mpox vaccination may reduce mpox incidence and mpox disease severity. It is also associated with minimal risk of adverse effects. The overall certainty of the evidence is very low.

The overall certainty of evidence is **very low**.

Review Methods

A systematic search was done from the date of last search November 5, 2024 until February 15, 2025 using Medline, EMBASE, CENTRAL, Clintrials.gov and Google Scholar with a combined MeSH and free text search using primarily the terms, 'monkeypox', 'mpox', 'monkeypox vaccination', 'high risk individuals'.

Eligible studies of this review were observational studies, case-control studies, cohort studies and randomized and non-randomized controlled trials evaluating the safety, efficacy and cost-effectiveness of ACAM2000, MVA-BN vaccines and LC16 compared to no vaccination in high-risk individuals. Evidence from existing high-quality guidelines (based on AGREE-II tool) were also adopted. We excluded animal, pre-clinical studies and studies that included healthy subjects. Articles in different languages and studies, which included vaccines given as pre-exposure prophylaxis and post-exposure prophylaxis, were included. Outcomes of interest include efficacy outcomes (incidence of mpox, severity of mpox, vaccine effectiveness, immunogenicity), adverse effects and cost-effectiveness. Subgroup analysis based on pre-exposure prophylaxis, post-exposure prophylaxis and the type of vaccine was also performed.

Recommendations from Other Groups

Various health authorities recommend mpox vaccination for individuals at high risk of exposure, including as pre-exposure prophylaxis for those at ongoing risk and post-exposure prophylaxis for recent contacts. Guidelines from agencies such as ATAGI, NACI, WHO, CDC, and state health departments support vaccination during outbreaks and for specific groups, including those with occupational exposure, emphasizing a 2-dose JYNNEOS series where applicable. In the 2023 Philippine Guidelines on Period Health Examination (PHEX) for Immunization in Adults, mpox vaccination was not recommended for individuals at high risk of exposure due to the very low certainty of evidence and difficulties with vaccine access and implementation.

Group or Agency	Recommendations
Australian Technical Advisory Group on Immunization, ATAGI, 2022	**Pre-exposure prophylaxis:** People at risk of exposure to mpox are recommended to receive mpox vaccine **Post-exposure prophylaxis:** People who are categorised by public health authorities as a high-risk mpox contact in the past 14 days are recommended to receive mpox vaccine.
National Advisory Committee on Immunization, NACI, 2022	Mpox vaccination is recommended for people at risk of contacting mpox, especially during an outbreak
WHO Emergence Response, Immunization, Vaccines and Biologics, Strategic Advisory Group of Experts on Immunization, WHO SAGE, 2022	Vaccination is recommended for groups at high risk for exposure to monkeypox Children, pregnant women and immunocompromised persons are not at risk of developing severe disease
Vaccine for Mpox Prevention in the United States, CDC, 2024	People at risk of mpox should be vaccinated prior to exposure to *Monkeypox virus*. People may be vaccinated after exposure to *Monkeypox virus* to help prevent mpox (i.e. post-exposure prophylaxis)
Prevention and Treatment of Mpox: Clinical Guidelines Program, New York, State Department of Health AIDS Institute, 2024	Mpox immunization for primary prevention is recommended for individuals at elevated risk of infection
Interim Clinical Considerations for Use of Vaccine for Mpox Prevention in the United States, CDC, 2025	The Advisory Committee on Immunization Practices (ACIP) recommends the 2-dose JYNNEOS series to several populations • For pre-exposure vaccination of people at risk for occupational exposure to orthopoxviruses For people aged 18 years and older at risk of mpox during an mpox outbreak
2023 Philippine Guidelines on Periodic Health Examination: Immunization for Adults (02 Sep 2023)	Among adults with high risk* of exposure to monkeypox, we suggest AGAINST giving monkeypox vaccine. (Very low certainty of evidence, weak recommendation) **Healthcare workers responding to monkeypox outbreak, laboratory personnel who are handling monkeypox virus, people with multiple sexual partners, men having sex with men (MSM)*

Note: No strength of recommendation and certainty of evidence available.

Ongoing Studies and Research Gaps

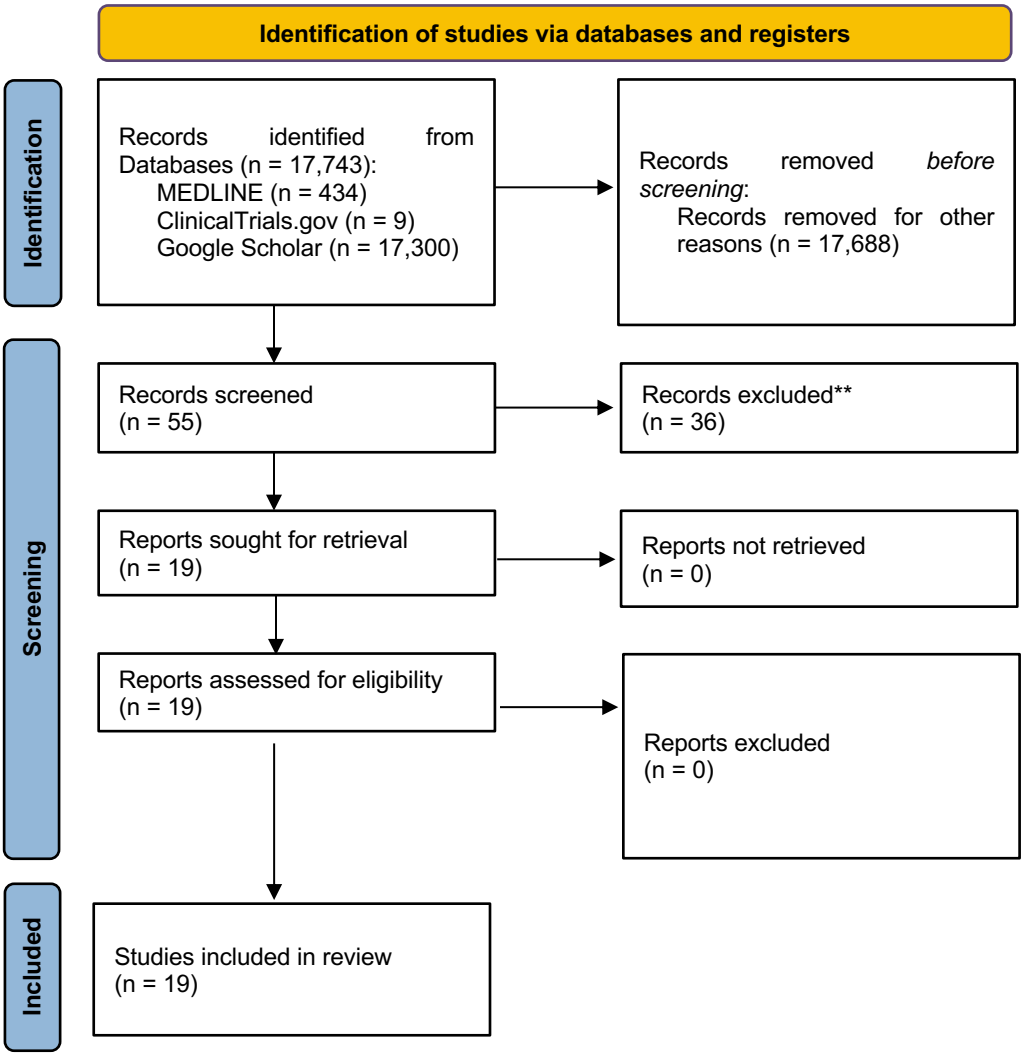
A Japanese open-labeled, single-armed study by Yano et al, aims to evaluate the efficacy and safety of LC16m8 strain vaccine in patients with close contacts to infected patients as post-exposure prophylaxis. (DERR1-10.196/46955; Japan Registry of Clinical Trials jRCTs031220137). Target completion date is not reported.

Search Strategy

Database	Search Strategy / Search Terms	Date and Time of Search	Results	
			Yield	Eligible
MEDLINE	(("health personnel"[MeSH Terms] OR ("health"[All Fields] AND "personnel"[All Fields]) OR "health personnel"[All Fields] OR ("healthcare"[All Fields] AND "workers"[All Fields]) OR "healthcare workers"[All Fields] OR ("immunocompromisation"[All Fields] OR "immunocompromise"[All Fields] OR "immunocompromised host"[MeSH Terms] OR ("immunocompromised"[All Fields] AND "host"[All Fields]) OR "immunocompromised host"[All Fields] OR "immunocompromised"[All Fields] OR "immunocompromising"[All Fields]) OR (("men"[MeSH Terms] OR "men"[All Fields]) AND ("sex"[MeSH Terms] OR "sex"[All Fields]) AND ("men"[MeSH Terms] OR "men"[All Fields])) OR ("mens sana monogr"[Journal] OR "mater sociomed"[Journal] OR "msm"[All Fields]) OR ("pregnant"[All Fields] OR "pregnants"[All Fields]) OR ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s"[All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields]) OR ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields] OR "infant s"[All Fields])) AND ("smallpox vaccine"[MeSH Terms] OR ("smallpox"[All Fields] AND "vaccine"[All Fields]) OR "smallpox vaccine"[All Fields] OR ("monkeypox"[All Fields] AND "vaccine"[All Fields]) OR "monkeypox vaccine"[All Fields] OR ("smallpox vaccine"[MeSH Terms] OR ("smallpox"[All Fields] AND "vaccine"[All Fields]) OR "smallpox vaccine"[All Fields] OR ("mpox"[All Fields] AND "vaccine"[All Fields]) OR "mpox vaccine"[All Fields]) OR ("acam2000"[Supplementary Concept] OR "acam2000"[All Fields] OR "acam2000"[All Fields]) OR (("modifiable"[All Fields] OR "modified"[All Fields] OR "modifier"[All Fields] OR "modifiers"[All Fields] OR "modifies"[All Fields] OR "modify"[All Fields] OR "modifying"[All Fields]) AND ("vaccinia"[MeSH Terms] OR "vaccinia"[All Fields] OR "vaccinia virus"[MeSH Terms] OR ("vaccinia"[All Fields] AND "virus"[All Fields]) OR "vaccinia virus"[All Fields] OR "vaccinias"[All Fields]) AND "Ankara-Bavarian"[All Fields] AND ("nordic"[All Fields] OR "nordics"[All Fields]) AND ("vaccin"[Supplementary Concept] OR "vaccin"[All Fields] OR "vaccination"[MeSH Terms] OR "vaccination"[All Fields] OR "vaccinable"[All Fields] OR "vaccinal"[All Fields] OR "vaccinate"[All Fields] OR "vaccinated"[All Fields] OR "vaccinates"[All Fields] OR "vaccinating"[All Fields] OR "vaccinations"[All Fields] OR "vaccination s"[All Fields] OR "vaccinator"[All Fields] OR "vaccinators"[All Fields] OR "vaccine s"[All Fields] OR "vaccined"[All Fields] OR "vaccines"[MeSH Terms] OR "vaccines"[All Fields] OR "vaccine"[All Fields] OR "vaccins"[All Fields])) OR (("smallpox and monkeypox vaccine modified vaccinia ankara bavarian nordic"[Supplementary Concept] OR "smallpox and monkeypox vaccine modified vaccinia ankara bavarian nordic"[All Fields] OR "mva bn"[All Fields]) AND ("vaccin"[Supplementary Concept] OR "vaccin"[All Fields] OR "vaccination"[MeSH Terms] OR "vaccination"[All Fields] OR "vaccinable"[All Fields] OR "vaccinal"[All Fields] OR "vaccinate"[All Fields] OR "vaccinated"[All Fields] OR "vaccinates"[All Fields] OR "vaccinating"[All Fields] OR "vaccinations"[All Fields] OR "vaccination s"[All Fields] OR "vaccinator"[All Fields] OR "vaccinators"[All Fields] OR "vaccine s"[All Fields] OR "vaccined"[All Fields] OR "vaccines"[MeSH Terms] OR "vaccines"[All Fields] OR "vaccine"[All Fields] OR "vaccins"[All Fields])) OR ("smallpox and monkeypox vaccine modified vaccinia ankara bavarian nordic"[Supplementary Concept] OR "smallpox and monkeypox vaccine modified vaccinia ankara bavarian nordic"[All Fields] OR "jynneos"[All Fields] OR "vaccinia virus"[MeSH Terms] OR ("vaccinia"[All Fields] AND "virus"[All Fields]) OR "vaccinia virus"[All Fields]) OR ("smallpox and monkeypox vaccine modified vaccinia ankara bavarian nordic"[Supplementary Concept] OR "smallpox and monkeypox vaccine modified vaccinia ankara bavarian nordic"[All Fields] OR "imvamune"[All Fields]) OR ("smallpox and monkeypox vaccine	February 15, 2025 2100H	434	19

Database	Search Strategy / Search Terms	Date and Time of Search	Results	
			Yield	Eligible
	modified vaccinia ankara bavarian nordic"[Supplementary Concept] OR "smallpox and monkeypox vaccine modified vaccinia ankara bavarian nordic"[All Fields] OR "imvanex"[All Fields]) OR "LC16m8"[All Fields]) AND ("prevent"[All Fields] OR "preventability"[All Fields] OR "preventable"[All Fields] OR "preventative"[All Fields] OR "preventatively"[All Fields] OR "preventatives"[All Fields] OR "prevented"[All Fields] OR "preventing"[All Fields] OR "prevention and control"[MeSH Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prevention"[All Fields] OR "prevention s"[All Fields] OR "preventions"[All Fields] OR "preventive"[All Fields] OR "preventively"[All Fields] OR "preventives"[All Fields] OR "prevents"[All Fields] OR ("safety"[MeSH Terms] OR "safety"[All Fields] OR "safeties"[All Fields]) OR (("adverse"[All Fields] OR "adversely"[All Fields] OR "adverses"[All Fields]) AND ("outcome"[All Fields] OR "outcomes"[All Fields])) OR ("adverse effects"[MeSH Subheading] OR ("adverse"[All Fields] AND "effects"[All Fields]) OR "adverse effects"[All Fields] OR ("side"[All Fields] AND "effects"[All Fields]) OR "side effects"[All Fields]) OR ("seroconversion"[MeSH Terms] OR "seroconversion"[All Fields] OR "seroconversions"[All Fields]) OR ("antigens"[MeSH Terms] OR "antigens"[All Fields] OR "immunogen"[All Fields] OR "immunogens"[All Fields] OR "immunogene"[All Fields] OR "immunogeneic"[All Fields] OR "immunogenes"[All Fields] OR "immunogenic"[All Fields] OR "immunogenically"[All Fields] OR "immunogenicities"[All Fields] OR "immunogenicity"[All Fields] OR "immunogenity"[All Fields]) OR ("cost effectiveness analysis"[MeSH Terms] OR ("cost effectiveness"[All Fields] AND "analysis"[All Fields]) OR "cost effectiveness analysis"[All Fields] OR ("cost"[All Fields] AND "effectiveness"[All Fields]) OR "cost effectiveness"[All Fields]))) AND (2018:2025[pdat])			
ClinicalTrials.gov	Monkeypox; Vaccine; High risk patients	February 14, 2025 1900H	9	0
Google Scholar	Effect of vaccines in High Risk Patients on Monkeypox	February 15, 2025 2100H	17,300	0

PRISMA Flow Diagram



Included Studies

Characteristics of Included Studies

Author / Year	Study Design	Country	Total Participants	Population	Intervention	Control	Outcomes	Duration of follow-up
Farrar et al, 2022	Retrospective observational study	USA	6605 (Vaccinated = 276, Unvaccinated = 6329)	Adults at risk who developed mpox	MVA-BN 1 dose	No vaccine	Efficacy outcome -Incidence of mpox	4 months
Merad et al, 2022	Retrospective observational study	France	108	Adults who experienced direct and indirect contact or prolonged exposure to an mpox case	MVA-BN 1 dose and 2 doses, 4 weeks apart	No control	Efficacy outcome -Breakthrough mpox	2 months
Payne et al, 2022	Prospective cohort study	USA	9544 (Vaccinated = 1224, Unvaccinated = 8320)	Adult males who participate in MSM, living with HIV	MVA-BN 1 dose and 2 doses, 4 weeks apart	No vaccine	Efficacy outcome -Illness onset	3 months
Thy et al, 2022	Prospective observational study	USA	276 (Vaccinated = 276)	Adults with high-risk mpox exposure	MVA-BN 1 dose (post-exposure prophylaxis	No control	Efficacy outcome -Incidence of mpox	2 months
Dalton et al, 2023	Case-control study	USA	917 (Case = 309, Control = 608)	Adults aged 18-49 years who self-identified as MSM or transgender that are sexually active	MVA-BN 1 dose and 2 doses, 4 weeks apart (pre-exposure prophylaxis)	No vaccine	Efficacy outcome -Vaccine effectiveness	7 months
Deputy et al, 2023	Case-control study	USA	10512 (Case = 2193, Control = 8319)	Adult patients seeking health care	MVA-BN 1 dose and 2 doses, 4 weeks apart (post-exposure prophylaxis)	No vaccine	Efficacy outcome -Vaccine effectiveness	3 months
Faherty et al, 2023	Prospective, observational study	USA	40 (Vaccinated with 2 doses of MVA-BN or 1 dose of live attenuated smallpox vaccine = 22, Vaccinated with 1 dose of MVA-BN or unvaccinated = 18)	Adult males with HIV or living with HIV	MVA-BN 2 doses or Live attenuated smallpox vaccine 1 dose	MVA-BN 1 dose or No vaccine	Efficacy outcome -Incidence of mpox	3 months
Faherty et al, 2023	Retrospective, observational study	USA	40 (Vaccinated = 15, Unvaccinated = 25)	Adult patients who attended Market Days, an annual LGBTQ outdoor festival	MVA-BN 1 dose	No vaccine	Efficacy outcome -Incidence of mpox	21 days
Ladhani et al, 2023	Prospective, observational study	United Kingdom	87	Children	MVA-BN 1 dose (post-exposure prophylaxis)	No control	Efficacy outcome -Immunogenicity Adverse effects	5 months

Author / Year	Study Design	Country	Total Participants	Population	Intervention	Control	Outcomes	Duration of follow-up
Morales et al, 2023	Prospective cohort study	Spain	484 (Vaccinated = 230, Unvaccinated = 254)	Adults with close contacts to an mpox case	MVA-BN 1 dose (post-exposure prophylaxis)	No vaccine	Efficacy outcome -Vaccine effectiveness	3 months
Ramchandani et al, 2023	Retrospective cohort study	USA	204 Vaccinated 1 dose = 11 Vaccinated 2 dose = 2 Unvaccinated = 191	Adults males with mpox who have sex with men	MVA-BN 1 dose, 2 dose (pre-exposure prophylaxis)	No vaccine	Efficacy outcome -Incidence of mpox	12 months
Sagy et el, 2023	Retrospective cohort study	Israel	2054 (Vaccinated = 1037, Unvaccinated =	Adult males with HIV/AIDS or with recent sexually transmitted infection	MVA-BN 1 dose and 2 doses, 4 weeks apart (pre-exposure prophylaxis)	No vaccine	Efficacy outcome -Vaccine effectiveness	141 days
Tomita et al, 2023	Prospective observational study	Japan	6	Patients with close contacts with mpox	Freeze-dried cell culture Smallpox vaccine LC16 (post-prophylaxis)	No control	Efficacy outcome -Incidence of mpox Adverse effects	28 days
Van Ewijk et al, 2023	Retrospective observational study	Netherlands	290 (Vaccinated = 223, Unvaccinated = 41)	Adults with high risk contact with mpox	MVA-BN 1 dose (post-exposure prophylaxis)	No vaccine	Efficacy outcome -Incidence of mpox	2 months
Brousseau et al, 2024	Case-control study	Canada	532	Adult males with high mpox risk	MVA-BN 1 dose (post-exposure prophylaxis)	No vaccine	Efficacy outcome -Vaccine effectiveness	3 months
Fontàn-Vela et al, 2024	Retrospective cohort study	Spain	11320 (Vaccinated = 5660, Unvaccinated = 5660)	Adult males receiving HIV-PrEP with no prior MPXV infection or MVA-BN vaccination	MVA-BN 1 dose (pre-exposure prophylaxis)	No vaccine	Efficacy outcome -Vaccine effectiveness	62 days
Ghosh et al, 2024	Prospective, multicenter, two-by-two factorial, randomized open-label, phase 3 trial	France	472 (Participants with mpox = 77 Mpox-free participants = 395)	Adults identified as MSM, HIV negative, who received HIV PrEP for at least 6 months and have a history of bacterial STIs within 12 months before enrollment	MVA-BN 1 dose and 2 doses, 4 weeks apart (post-exposure prophylaxis)	No vaccine	Efficacy outcome -Incidence of mpox	4 months
Navarro et al, 2024	Emulation of a target trial	Canada	9803	Adult males with history of being tested for syphilis and a laboratory confirmed bacterial sexually transmitted infection (STI) in previous year, or who filled a prescription for HIV pre-exposure prophylaxis in previous year	MVA-BN 1 dose (pre-exposure prophylaxis)	No vaccine	Efficacy outcome -Vaccine effectiveness	153 days

Author / Year	Study Design	Country	Total Participants	Population	Intervention	Control	Outcomes	Duration of follow-up
Rosen et al, 2024	Observational study	USA	549	Adults with high-risk or intermediate risk exposure to a person with confirmed or probably mpox disease	MVA-BN 1 dose (post-exposure prophylaxis)	No control	Efficacy outcome -Vaccine effectiveness	3 months

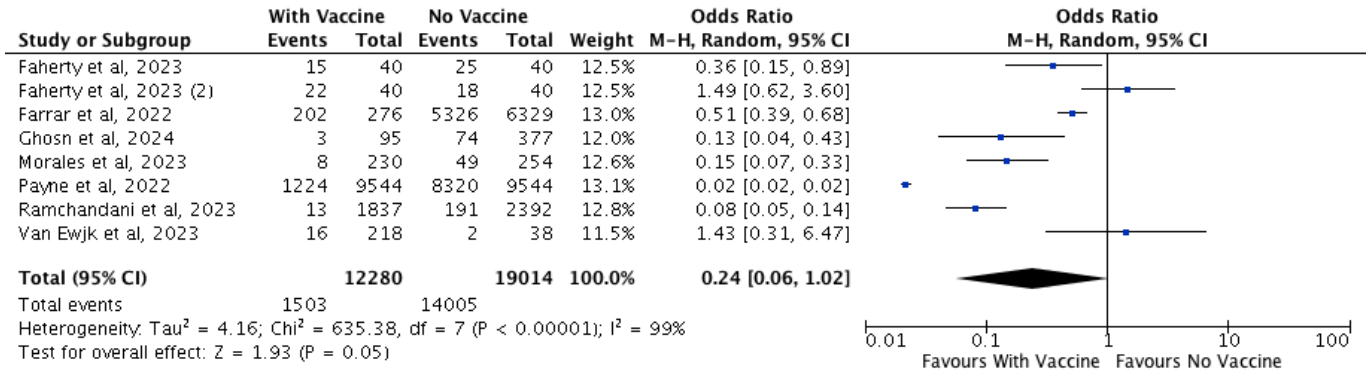
Quality Assessment of Included Studies

Study	Study Design	Confounding	Classification of Interventions	Selection of Participants	Deviations from Intended Interventions	Missing Data	Measurement of the Outcome	Selection of the Reported Result	Overall
Farrar et al, 2022	Retrospective observational study	High	Low	High	Low	Low	Low	Low	High
Merad et al, 2022	Retrospective observational study	High	Low	High	Low	Low	Low	Low	High
Payne et al, 2022	Prospective cohort study	High	Low	High	Low	Low	Low	Low	High
Thy et al, 2022	Prospective observational study	High	Low	High	Low	Low	Low	Low	High
Dalton et al, 2023	Case-Control Study	High	Low	Moderate	Low	Low	Low	Low	High
Deputy et al, 2023	Case-Control Study	High	Low	Moderate	Low	Low	Low	Low	High
Faherty et al, 2023	Prospective observational study	High	Low	High	Low	Low	Low	Low	High
Faherty et al, 2023 (2)	Retrospective observational study	High	Low	High	Low	Low	Low	Low	High
Ladhani et al, 2023	Prospective observational study	High	Low	High	Low	Low	Low	Low	High
Morales et al, 2023	Prospective cohort study	High	Low	High	Low	Low	Low	Low	High
Ramchandani et al, 2023	Retrospective cohort study	High	Low	High	Low	Low	Low	Low	High
Sagy et al, 2023	Retrospective cohort study	High	Low	High	Low	Low	Low	Low	High
Tomita et al, 2023	Prospective cohort study	High	Low	High	Low	Low	Low	Low	High
Van Ewijk et al, 2023	Retrospective observational study	High	Low	High	Low	Low	Low	Low	High
Brousseau et al, 2024	Case Control Study	High	Low	Moderate	Low	Low	Low	Low	High
Fontan-Vela et al, 2024	Retrospective cohort study	High	Low	High	Low	Low	Low	Low	High

Study	Study Design	Confounding	Classification of Interventions	Selection of Participants	Deviations from Intended Interventions	Missing Data	Measurement of the Outcome	Selection of the Reported Result	Overall
Ghosn et al, 2024	Prospective, randomized, open-label trial	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Navarro et al, 2024	Emulation of a target trial	High	Low	High	Low	Low	Low	Low	High
Roesen et al, 2024	Observational study	High	Low	High	Low	Low	Low	Low	High

Forest Plots

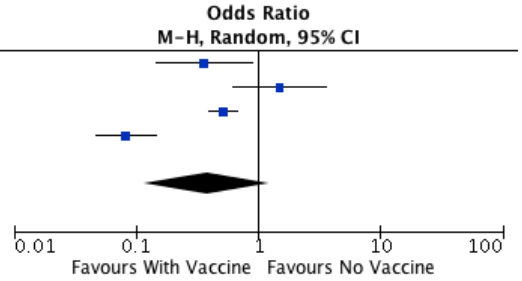
Incidence of Mpox



Incidence of Mpox with pre-exposure prophylaxis

Study or Subgroup	With Vaccine Events	With Vaccine Total	No Vaccine Events	No Vaccine Total	Weight	Odds Ratio M-H, Random, 95% CI
Faherty et al, 2023	15	40	25	40	23.5%	0.36 [0.15, 0.89]
Faherty et al, 2023 (2)	22	40	18	40	23.7%	1.49 [0.62, 3.60]
Farrar et al, 2022	202	276	5326	6329	27.0%	0.51 [0.39, 0.68]
Ramchandani et al, 2023	13	1837	191	2392	25.7%	0.08 [0.05, 0.14]
Total (95% CI)		**2193**		**8801**	**100.0%**	**0.38 [0.12, 1.23]**
Total events	252		5560			

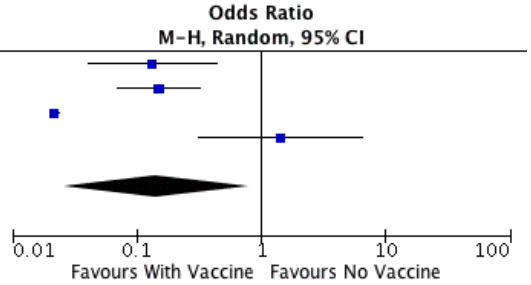
Heterogeneity: $Tau^2 = 1.31$; $Chi^2 = 47.74$, df = 3 ($P < 0.00001$); $I^2 = 94\%$
Test for overall effect: Z = 1.62 (P = 0.11)



Incidence of Mpox with Post-Exposure Prophylaxis

Study or Subgroup	With Vaccine Events	With Vaccine Total	No Vaccine Events	No Vaccine Total	Weight	Odds Ratio M-H, Random, 95% CI
Ghosn et al, 2024	3	95	74	377	24.2%	0.13 [0.04, 0.43]
Morales et al, 2023	8	230	49	254	25.9%	0.15 [0.07, 0.33]
Payne et al, 2022	1224	9544	8320	9544	27.3%	0.02 [0.02, 0.02]
Van Ewijk et al, 2023	16	218	2	38	22.5%	1.43 [0.31, 6.47]
Total (95% CI)		**10087**		**10213**	**100.0%**	**0.14 [0.03, 0.79]**
Total events	1251		8445			

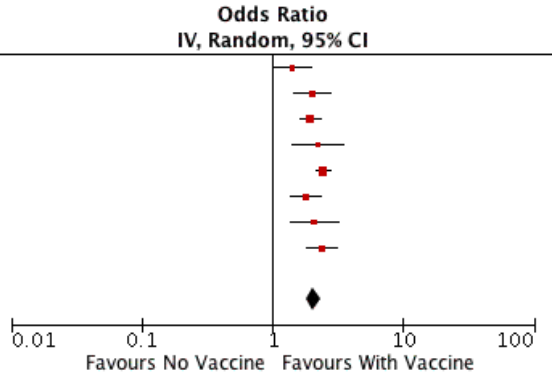
Heterogeneity: $Tau^2 = 2.77$; $Chi^2 = 62.58$, df = 3 ($P < 0.00001$); $I^2 = 95\%$
Test for overall effect: Z = 2.24 (P = 0.03)



Vaccine Effectiveness

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Brousseau et al, 2024	0.35	0.1684	10.0%	1.42 [1.02, 1.97]
Dalton et al, 2023	0.702	0.1648	10.3%	2.02 [1.46, 2.79]
Deputy et al, 2023	0.66	0.0949	18.2%	1.93 [1.61, 2.33]
Fontan Vela et al, 2024	0.79	0.2332	6.2%	2.20 [1.40, 3.48]
Morales et al, 2023	0.888	0.0653	22.7%	2.43 [2.14, 2.76]
Navarro et al, 2024	0.58	0.1378	12.8%	1.79 [1.36, 2.34]
Rosen et al, 2024	0.73	0.2143	7.1%	2.08 [1.36, 3.16]
Sagy et al, 2023	0.86	0.1378	12.8%	2.36 [1.80, 3.10]
Total (95% CI)			**100.0%**	**2.04 [1.80, 2.32]**

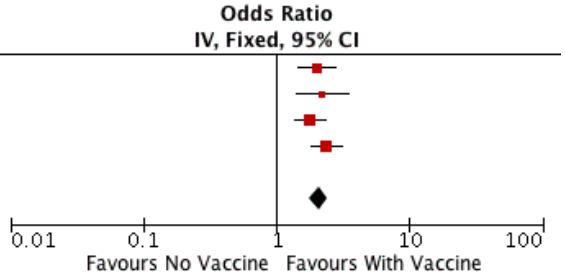
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 13.27$, df = 7 ($P = 0.07$); $I^2 = 47\%$
Test for overall effect: Z = 10.89 ($P < 0.00001$)



Vaccine Effectiveness with Pre-Exposure Prophylaxis

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Dalton et al, 2023	0.702	0.1648	22.9%	2.02 [1.46, 2.79]
Fontan Vela et al, 2024	0.79	0.2332	11.5%	2.20 [1.40, 3.48]
Navarro et al, 2024	0.58	0.1378	32.8%	1.79 [1.36, 2.34]
Sagy et al, 2023	0.86	0.1378	32.8%	2.36 [1.80, 3.10]
Total (95% CI)			**100.0%**	**2.06 [1.77, 2.41]**

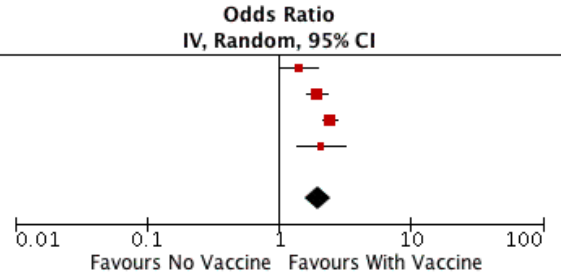
Heterogeneity: $Chi^2 = 2.16$, df = 3 (P = 0.54); $I^2 = 0\%$
Test for overall effect: Z = 9.17 (P < 0.00001)



Vaccine Effectiveness with Post-Exposure Prophylaxis

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Brousseau et al, 2024	0.35	0.1684	20.6%	1.42 [1.02, 1.97]
Deputy et al, 2023	0.66	0.0949	29.8%	1.93 [1.61, 2.33]
Morales et al, 2023	0.888	0.0653	33.5%	2.43 [2.14, 2.76]
Rosen et al, 2024	0.73	0.2143	16.1%	2.08 [1.36, 3.16]
Total (95% CI)			**100.0%**	**1.98 [1.59, 2.47]**

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 10.86$, df = 3 (P = 0.01); $I^2 = 72\%$
Test for overall effect: Z = 6.04 (P < 0.00001)



GUIDELINE QUESTION 11: Should antiviral medications and immunoglobulins be given to patients with confirmed mpox infection?

Research Question: Among patients with confirmed mpox infection, how effective and safe are antiviral medications and immunoglobulins?	
Population	Patients with confirmed mpox infection
Intervention / Treatment	Antiviral medications (tecovirimat, brincidofovir, cidofovir); immunoglobulins (vaccinia)
Comparator	No antivirals, no immunoglobulins, or supportive care
Outcomes	Resolution/Improvement of skin lesions; hospitalization; reduction of hospital stay; reduction of mortality due to mpox; all-cause mortality
Subgroups (if any)	Resolution/improvement of skin lesions; hospitalization; reduction of hospital stay; reduction of mortality due to mpox; all-cause mortality
Methods	RCTs, observational studies

Evidence Reviewers: Dr. Julian Mikhael A. Buban, Mr. Howell Henrian G. Bayona
Date of Last Search: February 28, 2025 (studies), April 10, 2025 (clinical trials)

Statement of the Evidence

Among patients with mpox, topical cidofovir is associated with decreased time to skin lesion resolution, with mild to moderate adverse effects in the skin. Oral tecovirimat does not significantly decrease time to symptom resolution, symptom improvement, or viral load among patients with mpox, with mild adverse effects. There is no available data regarding the antiviral effects and safety of brincidofovir and vaccinia immunoglobulin.

The overall certainty of the evidence is **very low**.

Review Methods

A database search of MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials with a combination of free-text and MeSH terms including "mpox," "tecovirimat," "brincidofovir," "cidofovir," and "vaccinia" was done to search for randomized controlled trials, cohort studies, systematic reviews, and meta-analyses that report the effect of tecovirimat, brincidofovir, cidofovir, and vaccinia immunoglobulin compared to placebo or standard of care in the management of mpox patients. Records of ongoing clinical trials were obtained by searching ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform. The final search dates were on February 28, 2025 for completed studies and April 10, 2025 for ongoing clinical trials.

No restrictions on patient mpox severity status, treatment outcome, country, or language were applied. Studies that were not original research, in-vitro studies, case-control studies and case series, studies combining the aforementioned drugs with other treatments, and those that compare these drugs to treatments that are not

placebo or standard of care were excluded. Included studies were appraised for risk of bias using the Newcastle-Ottawa Scale for cohort studies and cross-sectional studies.[29]

Data extracted included country, study design, patient profile, sample size (treatment and control groups), patient age and sex ratio, primary and secondary outcomes, and reported mean difference (MD) or hazard ratio (HR). Odds ratio (OR) estimates were generated using a random-effects generic inverse variance model in Review Manager 5.4 (Cochrane Collaboration) if adequate data was available.

Recommendations from Other Groups

Tecovirimat is authorized for mpox treatment in the European Union, while the United States CDC allows its use under expanded access, alongside other antivirals like brincidofovir, cidofovir, and vaccinia immunoglobulin. In contrast, the WHO and the Philippine Society for Microbiology and Infectious Diseases recommend limiting the use of these treatments to clinical trials or compassionate/expanded access settings due to insufficient evidence. All reviewed guidelines did not specify a strength of recommendation or certainty of evidence rating.

Group or Agency	Recommendation
European Medicines Agency[30] (accessed 27 April 2025)	Tecovirimat authorized in the European Union as treatment for mpox
United States Centers for Disease Control[31] (accessed 27 April 2025)	Tecovirimat available under expanded access protocol Brincidofovir, cidofovir, vaccinia immunoglobulin can be considered in combination with or as an alternative to tecovirimat
Philippine Society for Microbiology and Infectious Diseases[32] (published 8 September 2024)	Insufficient evidence to support the routine use of tecovirimat, brincidofovir, cidofovir, or vaccinia immunoglobulin except in the context of a clinical trial or for compassionate use.
World Health Organization[33] (published 10 June 2022)	Antivirals including tecovirimat, brincidofovir, cidofovir preferably for use under randomized clinical trials and, when not possible, under expanded access protocols Vaccinia immunoglobulin should be used in a clinical research context with prospective data collection

Ongoing Studies and Research Gaps

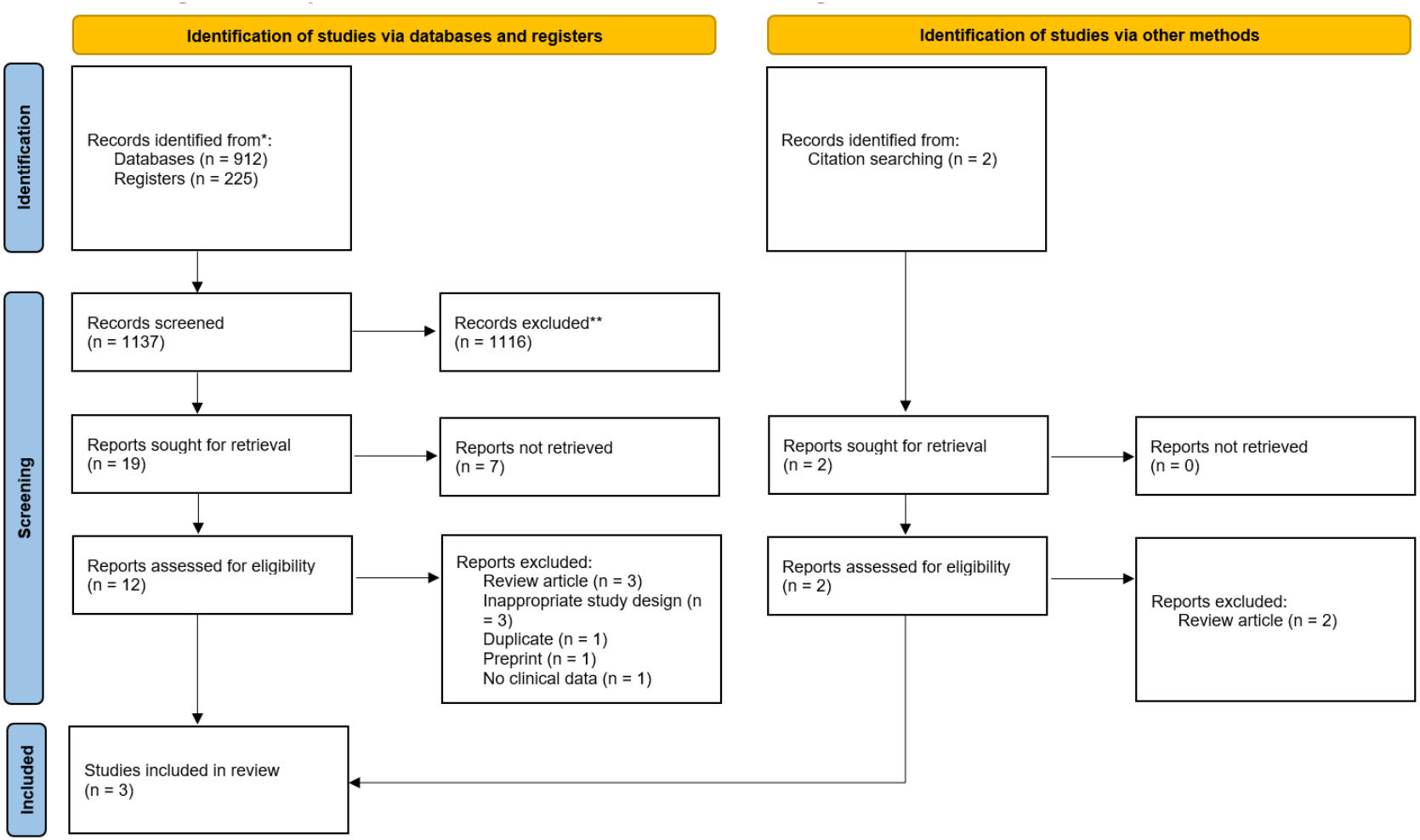
Eight clinical trials are currently ongoing or with pending results for the use of the aforementioned treatments for mpox; of these, six are for tecovirimat, one is for cidofovir (Japan), and one is for vaccinia immunoglobulin (Japan). Two of the ongoing trials involving tecovirimat, the PALM007 trial in the Democratic Republic of the Congo and the multinational STOMP trial, have published preliminary results, reporting that while the drug has a good safety profile, it does not significantly reduce the number of deaths or time to symptom resolution, or improve pain control compared to placebo in patients with mpox.[34,35]

[29] Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
[30] European Medicines Agency. Mpox [Internet]. 2025 [cited 25 April 2025]. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/public-health-threats/mpox
[31] Centers for Disease Control and Prevention. Clinical treatment of mpox [Internet]. 2025 [cited 25 April 2025]. Available from: https://www.cdc.gov/mpox/hcp/clinical-care/index.html
[32] Philippine Society for Microbiology and Infectious Diseases. Guidance on the management of mpox. 8 September 2024.
[33] World Health Organization. Clinical management and infection prevention and control for monkeypox: interim rapid response guidance. World Health Organization; 2022.
[34] National Institutes of Health. The antiviral tecovirimat is safe but did not improve clade I mpox resolution in Democratic Republic of the Congo [Internet]. 15 August 2024 [cited 25 April 2025]. Available from: https://www.nih.gov/news-events/news-releases/antiviral-tecovirimat-safe-did-not-improve-clade-i-mpox-resolution-democratic-republic-congo
[35] ACTG Network. ACTG presents data from mpox study STOMP at CROI [Internet]. 12 March 2025 [cited 25 April 2025]. Available from: https://www.globenewswire.com/news-release/2025/03/12/3041585/0/en/ACTG-Presents-Data-from-Mpox-Study-STOMP-at-CROI.html

Search Strategy

Database	#	Search Strategy / Search Terms	Date and Time of Search	Yield
Medline	#1	(mpox OR monkeypox) AND (tecovirimat OR brincidofovir OR cidofovir OR Tpoxx OR ST-246 OR Tembexa OR CMX001 OR vaccinia OR Vistide OR immunoglobulin OR "Ig" OR IgG)	February 28, 2025 10:00 AM	1249
	#2	(randomized clinical trial[Publication Type]) OR (randomized controlled trial[Publication Type]) OR (controlled clinical trial[Publication Type]) OR (randomized[Title/Abstract]) OR (randomised[Title/Abstract]) OR (trial[Title/Abstract]) OR (random[Title/Abstract]) OR (randomly[Title/Abstract]) OR (clinical trials as topic[MeSH Terms]) OR (controlled clinical trials as topic[MeSH Terms]) OR (controlled clinical trials, randomized[MeSH Terms])		2344005
	#3	(prospective[Title/Abstract]) OR (retrospective[Title/Abstract]) OR (observational[Title/Abstract]) OR (cohort[Title/Abstract]) OR (closed cohort studies[MeSH Terms]) OR (closed cohort study[MeSH Terms]) OR (analyses, cohort[MeSH Terms]) OR (analysis, cohort[MeSH Terms]) OR (cohort analyses[MeSH Terms])		3638769
	#4	#1 AND (#2 OR #3)		156
Embase	#1	monkeypox'/exp OR 'monkeypox'	February 28, 2025 12:00 PM	6229
	#2	mpox:ti,ab		2185
	#3	#1 OR #2		6654
	#4	tecovirimat'		1102
	#5	brincidofovir		1150
	#6	cidofovir		7969
	#7	tpoxx		82
	#8	st 246'		199
	#9	tembexa		21
	#10	cmx001		145
	#11	vaccinia		22143
	#12	vistide		492
	#13	immunoglobulin'		939732
	#14	ig		76066
	#15	immunoglobulin g'		287088
	#16	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15		1002681
	#17	#16 AND #3		2001
	#18	#16 AND #3 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)		62
	#19	#17 AND ('case control study'/de OR 'clinical trial'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'controlled study'/de OR 'cross sectional study'/de OR 'longitudinal study'/de OR 'major clinical study'/de OR 'observational study'/de OR 'prospective study'/de OR 'retrospective study'/de)		653
	#20	#17 AND ('randomized controlled trial'/de OR 'randomized controlled trial topic'/de)		40
CENTRAL	#1	((mpox OR monkeypox) AND (tecovirimat OR brincidofovir OR cidofovir OR Tpoxx OR ST-246 OR Tembexa OR CMX001 OR vaccinia OR Vistide OR immunoglobulin OR IgG)):ti,ab,kw		39
ClinicalTrials.gov	#1	(mpox OR monkeypox) AND (tecovirimat OR brincidofovir OR cidofovir OR Tpoxx OR ST-246 OR Tembexa OR CMX001 OR vaccinia OR Vistide OR immunoglobulin OR IgG)	April 10, 2025 10:00 AM	97
WHO ICTRP	#1	mpox OR monkeypox	April 10, 2025 10:30 AM	90

PRISMA Flow Diagram



Included Studies

Characteristics of Included Studies

Author Year	Study design	Country	No. of patients	Population	Intervention Group(s)	Control	Outcomes
Tecovirimat (2)							
Karmarkar 2022	Cross-sectional study	United States	156	Patients with laboratory-confirmed mpox	Tecovirimat, any route/dose	Standard of care	Primary: Time to symptom resolution (number of days between onset date and resolution of all symptoms and completely healed lesions and a new layer of skin) Secondary: Time to subjective symptom improvement (patient report of any subjective improvement in symptoms, which could include 'beginning to feel better", resolution of fever or chills, decreased pain of lesions, or any other health improvement)
Mazzotta 2023	Prospective cohort study	Italy	41	Adults hospitalized for PCR-diagnosed mpox	Tecovirimat 600 mg twice a day for 14 days	Standard of care	Primary: Time to recovery (time from symptom onset to complete healing of skin and mucosal lesions by Day 21) Secondary: Change in PCR cycle threshold (CT) from 5 days after start of treatment (T1) to a second time point where CT is detectable (T2)
Cidofovir (1)							
Sobral-Costas 2022	Prospective cohort study	Spain	24	Adults with PCR-diagnosed mpox and at least 1 skin lesion	Topical cidofovir 1% twice a day for 7 days	Standard of care	Primary: Time to symptom resolution Secondary: PCR positivity of swab samples from the skin lesion and the pharynx at days 7 and 14

Quality Assessment of Included Studies

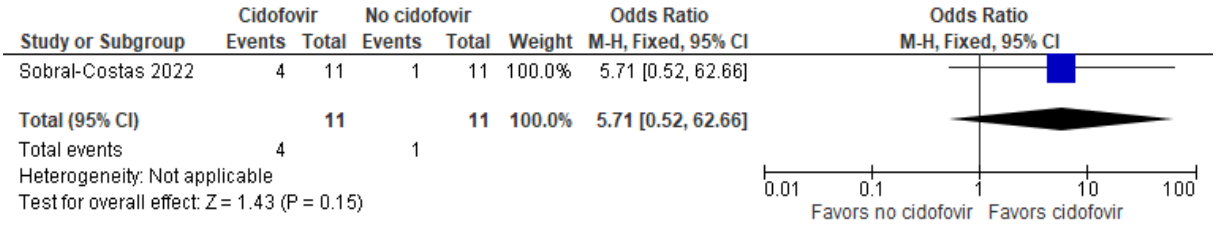
Risk of bias assessment of included studies (Newcastle-Ottawa Scale for non-randomized studies)

Criteria	Tecovirimat	Cidofovir	
	Karmarkar 2022	Mazzotta 2023	Sobral-Costas 2022
I. SELECTION			
1) Representativeness of the exposed cohort	*	*	*
2) Selection of the non-exposed cohort	*	*	*
3) Ascertainment of exposure	*	*	*
4) Demonstration that outcome of interest was not present at the start of the study	*	*	*
II. COMPARABILITY			
1) Comparability of cohorts on the basis of the design or analysis		*	**
III. OUTCOME			
1) Assessment of outcome		*	*
2) Was follow-up long enough for outcomes to occur	*	*	*
3) Adequacy of follow-up of cohorts	*	*	
TOTAL (out of 9*)	**6***	**8***	**8***

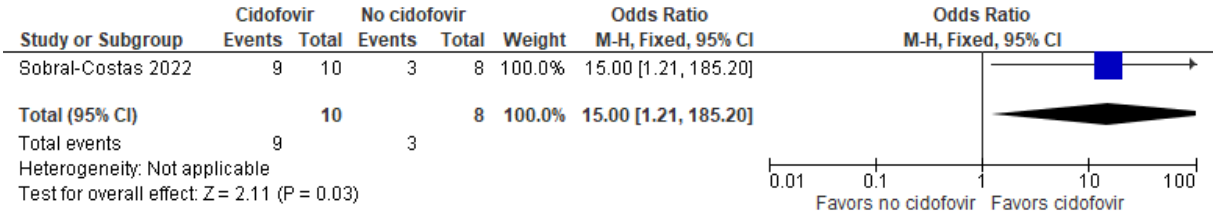
*" * " indicates that the criteria was met*

Forest Plots

Monkeypox PCR positivity in skin lesion samples (day 7)



Monkeypox PCR positivity in skin lesion samples (day 14)



Monkeypox PCR positivity in pharyngeal samples (day 7)