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

August 31, 2025

Disclaimer and Contact Information

This Clinical Practice Guideline (CPG) is intended to assist healthcare providers in the Philippines in the prevention, diagnosis, and management of selected Emerging and Re-emerging Infectious Diseases (EREID) specifically pertussis, leptospirosis, COVID-19 infection, mpox and avian influenza among children and adult population. Medical organizations and policy-making bodies may utilize this CPG in crafting local policies that address the negative impact of EREIDs.

Evidence summaries are based on the best available scientific evidence at the time of its formulation. As such, certain aspects of the interventions or diagnostic tests may not be completely addressed by the included studies.

This CPG does not aim to comprehensively address the management of all EREIDs. Rather, it provides recommendations on areas where clinical practices vary, and decision-making may be uncertain. Although adherence to this guideline is encouraged, it should not restrict the health care provider in using sound clinical judgment. Payors and policymakers, including hospital administrators and employers, should not use this guideline as the sole basis for evaluating insurance claims. Further, recommendations should also not be treated as strict rules on which to base legal action.

While every effort has been made to ensure the accuracy and relevance of the information, the authors and endorsing organizations assume no responsibility for any adverse outcomes or damages resulting from the application of this guideline.

Contact Information

For inquiries or clarifications regarding the output or development process of this CPG, you may contact us through email at rosemariearciaga3@gmail.com.

Acknowledgments

The development of the Clinical Practice Guidelines on Emerging and Re-emerging Infectious Diseases (EREID) was made possible through the support and collaboration of dedicated individuals and institutions.

We would like to express our deepest gratitude to the Department of Health (DOH) for providing the funding and institutional support for this initiative. Their commitment to strengthening health systems and improving clinical care for infectious diseases has been instrumental in the completion of this guideline.

We also acknowledge the Institutes of Clinical Epidemiology, National Institutes of Health, University of the Philippines Manila, under whose leadership and technical expertise this project was implemented. Their guidance throughout the guideline development process ensured the methodological rigor and scientific integrity of this document.

Our heartfelt appreciation goes to all members of the Guideline Development Group, technical experts, and various stakeholders who contributed their time, knowledge, and invaluable insights. Their dedication and collaborative spirit were vital in shaping these evidence-based recommendations.

Finally, we recognize the countless frontline healthcare providers and public health professionals whose experiences and unwavering service in the face of emerging and re-emerging infectious disease threats continue to inspire and guide our work.

Together, we hope that this guideline serves as a useful resource in improving the prevention, diagnosis, and management of emerging and re-emerging infectious diseases in the Philippines.

Participating Societies, Organizations, Agencies, and Institutions

Department of Health

University of the Philippines Manila National Institutes of Health

Philippine Association of Medical Technologists

Philippine Society for Microbiology

Philippine Pediatric Society, Inc.

Philippine Alliance of Patient Organizations

Philippine Society for Microbiology and Infectious Diseases

Philippine College of Physicians

Pediatric Infectious Disease Society of the Philippines

Philippine Society of Public Health Physicians

Table of Contents

List of Abbreviations

ACBT	Active cycle of breathing techniques
ACIP	Advisory Committee on Immunization Practices
AGREE	Appraisal of Guidelines for Research & Evaluation
AIR	Amygdala and insula retraining
aP	Acellular pertussis
BNP	B-type natriuretic peptide
CAR	Chimeric antigen receptor
CBT	Cognitive behavioral therapy
CD4	Cluster of differentiation 4
CDC	Centers for Disease Control and Prevention
CFR	Case fatality rate
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
Ct	Cycle threshold
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
EPI	Expanded Program on Immunization
EREID	Emerging and reemerging infectious disease
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
GBMSM	Gay, bisexual, and men who have sex with men
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HBOT	Hyperbaric oxygen therapy
HHE	Hypotonic, hyporesponsive episodes
HIV	Human immunodeficiency virus
HPAI	High pathogenicity avian influenza
HPV	Human papilloma virus
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
IFA	Immunofluorescence assay
IL-6	Interleukin-6
IMT	Inspiratory muscle training
IPV	Inactivated poliovirus vaccine
LDH	Lactate dehydrogenase
LGBTI	Lesbian, gay, bisexual, transgender, and intersex
LGU	Local government unit
MAT	Microscopic agglutination test
MD	Mean difference
MIS-C	Multisystem Inflammatory Syndrome in Children
MIS-N	Multisystem Inflammatory Syndrome in Neonates
MMR	Measles, mumps, and rubella
MPXV	Monkeypox virus
MSM	Men having sex with men
MVA-BN	Modified Vaccinia Ankara-Bavarian Nordic
NCR	National Capital Region
NT-proBNP	N-terminal pro-B-type natriuretic peptide
OR	Odds ratio
PBM	Photobiomodulation
PCR	Polymerase chain reaction
PICO	Population, Intervention, Comparison, and Outcome
PIDSP	Pediatric Infectious Disease Society of the Philippines
PSMID	Philippine Society for Microbiology and Infectious Diseases
PT	Physiotherapy
QALY	Quality-adjusted life year
RAT	Rapid antigen test
RCPCH	Royal College of Pediatrics and Child Health
RCT	Randomized controlled trial
RR	Risk ratio
RT-PCR	Reverse transcription polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TDCS	Transcranial direct current stimulation
TNF	Tumor necrosis factor
VE	Vaccine effectiveness
VUM	Variants under monitoring
WHO	World Health Organization
wP	Whole cell pertussis

List of Tables

List of Figures

Executive Summary

Emerging and re-emerging infectious diseases (EREIDs) such as COVID-19, leptospirosis, pertussis, avian influenza, and mpox continue to pose significant public health threats in the Philippines.

This CPG for EREID aims to develop and provide evidence-based recommendations to healthcare professionals, policymakers, and public health officials regarding the diagnosis, treatment, and prevention of selected EREIDs, namely: pertussis, leptospirosis, COVID-19 infection, mpox, and avian influenza among children and adult populations.

Evidence review experts conducted systematic reviews of current best available evidence and assessed the certainty of evidence using the GRADE approach. A multidisciplinary guideline panel formulated the recommendations during an *en banc* guideline panel meeting and delphi process where applicable. When high-quality evidence was lacking but guidance was warranted, good practice statements were provided. Recommendations were tailored to the Philippine healthcare context, considering resource constraints and population-specific factors.

This CPG presents 23 recommendations addressing prevention, diagnosis, and management strategies for COVID-19, leptospirosis, pertussis, avian influenza, and mpox. The majority of recommendations were based on low to very low certainty evidence, reflecting global and local research gaps. Notable areas of uncertainty include rehabilitative interventions for long COVID, prophylaxis for leptospirosis in vulnerable populations, and long-term effectiveness of newer COVID-19 vaccines. Strong recommendations were given for the diagnosis of multisystemic inflammatory syndrome in children and in neonates (MIS-C and MIS-N), as well as recommendations for pertussis vaccine, avian influenza diagnostics, and mpox treatment. Good practice statements were issued for non-pharmaceutical interventions for mpox such as quarantine and active surveillance.

The guideline highlights key research gaps, including the need for high-quality local data, improved diagnostics, and operational research to evaluate the effectiveness and feasibility of recommended interventions. Despite limitations in the evidence base, the guideline provides comprehensive, contextually appropriate recommendations to inform clinical and public health responses to priority EREIDs in the Philippines.

This CPG offers standardized, evidence-informed guidance for managing priority EREIDs in the Philippines. The guideline will be updated as new evidence emerges or as significant changes in disease trends or epidemiology occur, to ensure continued relevance, scientific accuracy, and responsiveness to public health needs.

Table 1 on the next page lists the 23 CPG recommendations.

Table 1. Summary of 23 recommendations.

№	Recommendation	Certainty of Evidence	Strength of Recommendation
Rehabilitation for Long Coronavirus Disease (COVID)			
1	We suggest the use of rehabilitative interventions in adults with long COVID symptoms.	Very Low	Weak
MIS-C Diagnosis			
2.1	We recommend the use of the following clinical parameters to increase suspicion of multisystem inflammatory syndrome in children: • history of COVID-19, and • fever of at least 3 days, and • any two of the following: gastrointestinal, cardiovascular, dermatological, conjunctivitis, respiratory symptoms	Low	Strong
2.2	We recommend the use of any of the following laboratory parameters to increase suspicion of multisystem inflammatory syndrome in children: • CRP, D-dimer, ESR, Ferritin, NT-proBNP, Troponin T	Low	Strong
2.3	We recommend the use of the following clinical parameters to increase suspicion of multisystem inflammatory syndrome in neonates: • history of COVID-19, and • any two of the following: cardiovascular, neurological, gastrointestinal symptoms, fever	Low	Strong
2.4	We recommend the use of any of the following laboratory parameters to increase suspicion of multisystem inflammatory syndrome in neonates: • CRP, IL-6, D-dimer, BNP, Troponin T, ferritin, LDH, NT-proBNP, procalcitonin	Low	Strong
2024–2025 COVID-19 Vaccines			
3	We suggest the use of 2024–2025 versions of monovalent COVID-19 vaccine for adults, adolescents, children, and immunocompromised individuals.	Very Low	Weak
Alternative Leptospirosis Prophylaxis			
4.1	We suggest the use of azithromycin as an alternative post-exposure prophylaxis for leptospirosis in adults.	Very Low	Weak
4.2	We suggest the use of amoxicillin as an alternative post-exposure prophylaxis for leptospirosis in adults.	Very Low	Weak
4.3	We recommend against the use of cephalosporin as an alternative post-exposure prophylaxis for leptospirosis in adults.	Very Low (no evidence)	Strong

№	Recommendation	Certainty of Evidence	Strength of Recommendation
Leptospirosis Prophylaxis for Children and Pregnant Women			
5.1	We suggest the use of azithromycin for children <8 years of age and pregnant women as post-exposure prophylaxis for leptospirosis.	Very Low	Weak
5.2	We suggest the use of amoxicillin for children <8 years of age and pregnant women as post-exposure prophylaxis for leptospirosis.	Very Low	Weak
5.3	We recommend against the use of cephalosporin for children <8 years of age and pregnant women as post-exposure prophylaxis for leptospirosis.	Very Low (no evidence)	Strong
Steroids, Cyclophosphamide, or Combination for Severe Leptospirosis			
6	We suggest against the use of prednisolone to prevent pulmonary hemorrhage and acute kidney injury for cases of severe leptospirosis.	Very Low	Weak
Acellular Pertussis Vaccines			
7	We recommend the use of acellular OR whole cell pertussis vaccines to prevent pertussis in infants.	Low	Strong
Avian Influenza Diagnostics			
8.1	We recommend the use of RT-PCR to confirm the diagnosis of avian influenza in suspected cases.	Very Low	Strong
8.2	We recommend against the use of RAT to confirm the diagnosis of avian influenza in suspected cases.	Very Low	Strong
Mpox Quarantine			
9.1	We suggest against mandatory quarantine for close contacts* of confirmed or suspected cases of mpox. **WHO definition of close contact (Aug 26, 2024)*	Very Low	Weak
9.2	**Good Practice Statement*** For close contacts** of suspected or confirmed cases of mpox, we suggest active surveillance of symptoms and avoid direct interaction with immunocompromised individuals*** for 21 days post-exposure. **This Good Practice Statement is based on expert consensus intended to support best practice but is not a mandatory recommendation.* ***WHO definition of close contact (Aug 26, 2024)* ****CDC definition (Sep 13, 2024)*	N/A	None
9.3	**Good Practice Statement*** We suggest 21-day quarantine for close contacts** of confirmed or suspected mpox cases in closed communities:	N/A	None

№	Recommendation	Certainty of Evidence	Strength of Recommendation
	• Jails, military barracks, orphanages, dormitories, nursing homes, homeless shelters, evacuation centers, and other similar settings **This Good Practice Statement is based on expert consensus intended to support best practice but is not a mandatory recommendation.* ***WHO definition of close contact (Aug 26, 2024)*		
Mpox Vaccination for High-Risk Individuals			
10	We suggest the use of mpox vaccines as pre-exposure and post-exposure prophylaxis for persons at risk*. **WHO definition of high risk individuals*	Very Low	Weak
Mpox Treatments			
11.1	We recommend against the use of tecovirimat for patients with confirmed mpox infection.	High	Strong
11.2	We suggest the use of topical cidofovir for patients with confirmed mpox infection.	Very Low	Weak
11.3	We recommend against the use of brincidofovir or vaccinia immunoglobulins for patients with confirmed mpox infection.	Very Low (no evidence)	Strong

Color Legend:

Recommend for (strong recommendation)
Recommend against (strong recommendation)
Suggest for (weak recommendation)
Suggest against (weak recommendation)

Chapter 1. Introduction

1.1. Background

Emerging and re-emerging infectious diseases (EREIDs) pose significant public health challenges in the Philippines and in the world. The impact of EREIDs is multifaceted, affecting public health, economies, and societies. These diseases can cause significant morbidity and mortality, overwhelming healthcare systems and requiring substantial medical resources. Outbreaks can disrupt trade, travel, and economic activities, leading to substantial financial losses. Infectious disease outbreaks can lead to fear, stigma, and social disruption, impacting community cohesion and mental health.

The dynamic nature of EREIDs, driven by factors such as globalization, climate change, urbanization, and antimicrobial resistance, necessitates the development of robust, evidence-based Clinical Practice Guidelines (CPGs) to guide healthcare professionals in the effective diagnosis, treatment, prevention, and management of these diseases. Towards this end, CPGs serve as essential tools in standardizing clinical practice, ensuring that healthcare providers have access to the latest and most effective medical knowledge. They help bridge the gap between research and practice, offering clear, actionable recommendations that can be consistently applied across diverse healthcare settings. For EREIDs, the timely development and regular updating of CPGs are particularly critical, given the rapid evolution of these diseases and the continuous influx of new scientific evidence.

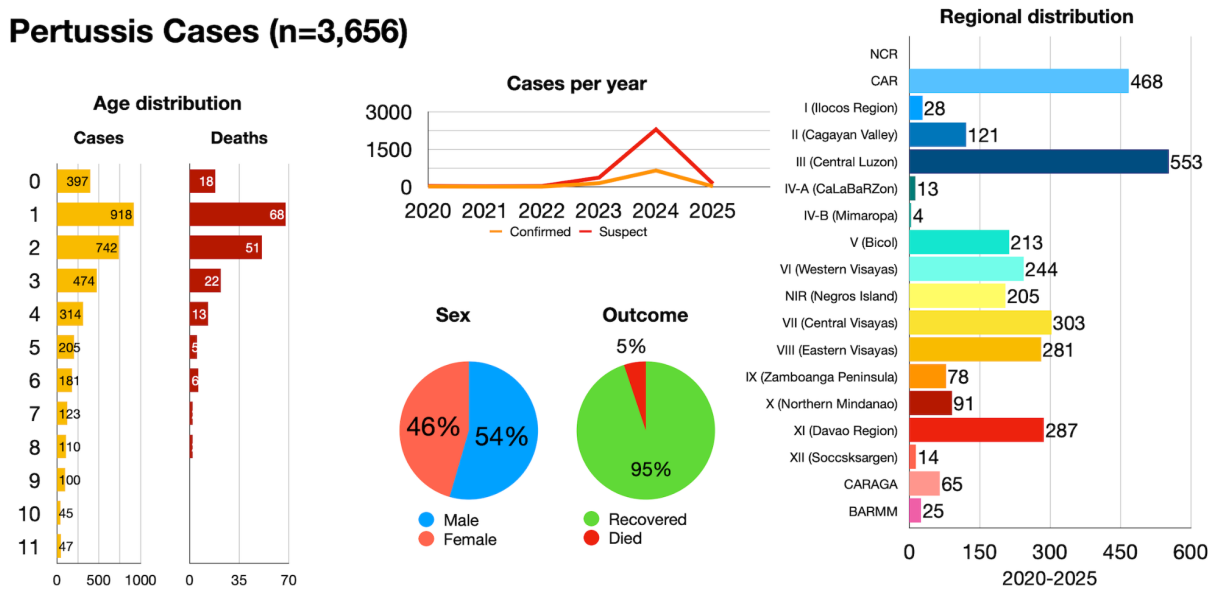
This CPG presents a structured approach to developing guidelines tailored for EREIDs in the Philippine context. It offers a comprehensive framework that ensures that the guidelines are based on the best available evidence and adaptable to the changing landscape of EREIDs. This CPG emphasizes the importance of multidisciplinary collaboration, stakeholder engagement, and adherence to rigorous methodological standards.

Identified Priority EREIDs

Among the identified priority EREIDs that have posed or may pose a significant impact in the Philippines are pertussis, leptospirosis, COVID-19 infection, avian influenza, and mpox.

Pertussis

A report from the Department of Health (DOH) showed a remarkable increase in the number of pertussis cases from 2022 to 2023 (42 cases vs 705 cases).[1] The increasing trend in the number of cases got even more pronounced in the first quarter of 2024 when the DOH recorded almost 1,000 cases (30 times that of the same period last year).[2] Cases were reportedly high in MIMAROPA, National Capital Region (NCR), Central Luzon, Central Visayas, and Western Visayas regions.

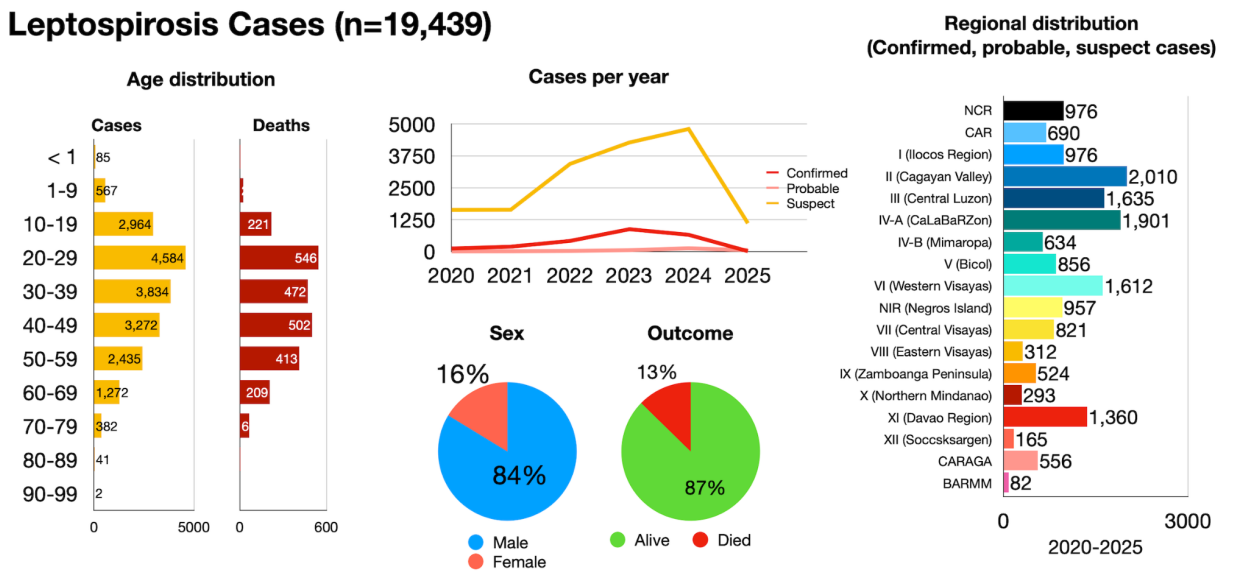


Source: Epidemiology Bureau, Department of Health (as of 02 May 2025)
Philippine Integrated Disease Surveillance and Response (PIDSR) Line-list - Pertussis 2020-2024 Annual Data and 2025 Data as of March 29, 2025 (MW13)
Data includes only cases of pertussis from 2020 to 2025. Reported deaths are unofficial and are used for surveillance purposes only.
The official source of mortality data is the Philippine Statistics Authority (PSA)

Figure 1. Epidemiology of pertussis in the Philippines from 2020 to 2025 (as of May 2, 2025).

Leptospirosis

Regarding leptospirosis, the Philippines experienced an increasing trend of leptospirosis cases and deaths since the outbreak in 2020. The year 2023 saw an alarming increase in cases—leptospirosis has been reported in almost all regions in the Philippines, but Cagayan Valley, Zamboanga Peninsula, and Western Visayas regions were the worst-hit that year.[3] Natural disasters like typhoons and floods are contributing factors to the rise in leptospirosis cases.[4] The most number of cases and deaths due to leptospirosis have been recorded in adults between 20-50 years old, especially in males.



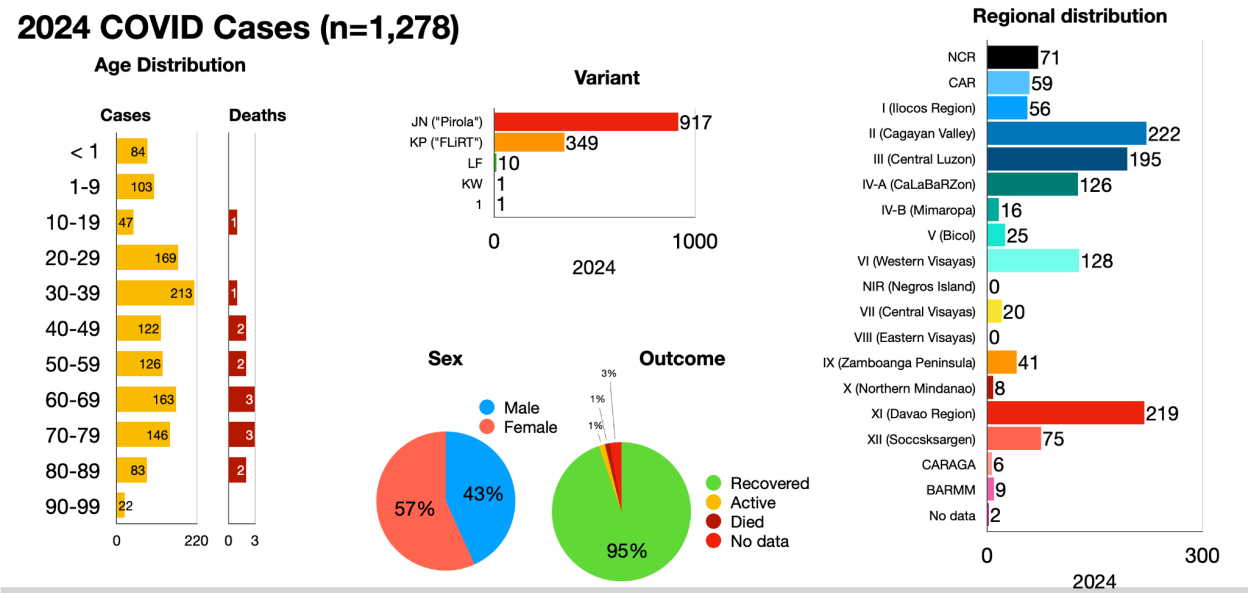
Source: Epidemiology Bureau, Department of Health (as of 02 May 2025)
Philippine Integrated Disease Surveillance and Response (PIDSR) Line-list - Leptospirosis 2020-2024 Annual Data and 2025 Data as of March 29, 2025 (MW13)
Data includes only cases of leptospirosis from 2020 to 2025. Reported deaths are unofficial and are used for surveillance purposes only.
The official source of mortality data is the Philippine Statistics Authority (PSA)

Figure 2. Epidemiology of leptospirosis in the Philippines from 2020 to 2025 (as of May 2, 2025).

COVID-19

As for coronavirus disease 2019 (COVID-19), the World Health Organization (WHO) declared the end of the COVID-19 pandemic in May 2023. The WHO stated that COVID-19 is no longer a public health emergency of international concern.[5,6] However, despite this declaration, COVID-19 remains a public health threat because even if the number of cases has significantly declined, new variants of the causative agent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are continuously being detected in several countries. Based on COVID-19 case data from the DOH Epidemiology Bureau, the JN variant was found to be causing most COVID cases in 2024, followed by the KP variant. In the United States for instance, the KP.2 variant and its parental strain JN.1 have been reported to be causing the latest COVID-19 infections.[7] In the Philippines, though the DOH has reported a slight increase in the number of cases, the country remains at low risk for COVID-19 transmission.[8]

Despite the low number of cases, there is a remaining concern regarding post-COVID clinical problems like long COVID and multisystem inflammatory syndrome in children or MIS-C. To date, long COVID is called by many names like long-haul COVID, post COVID conditions (PCC), post-acute COVID-19 or post-acute sequelae of SARS-CoV-2 infection (PASC). In this CPG, this clinical entity will still be referred to as 'long COVID'.

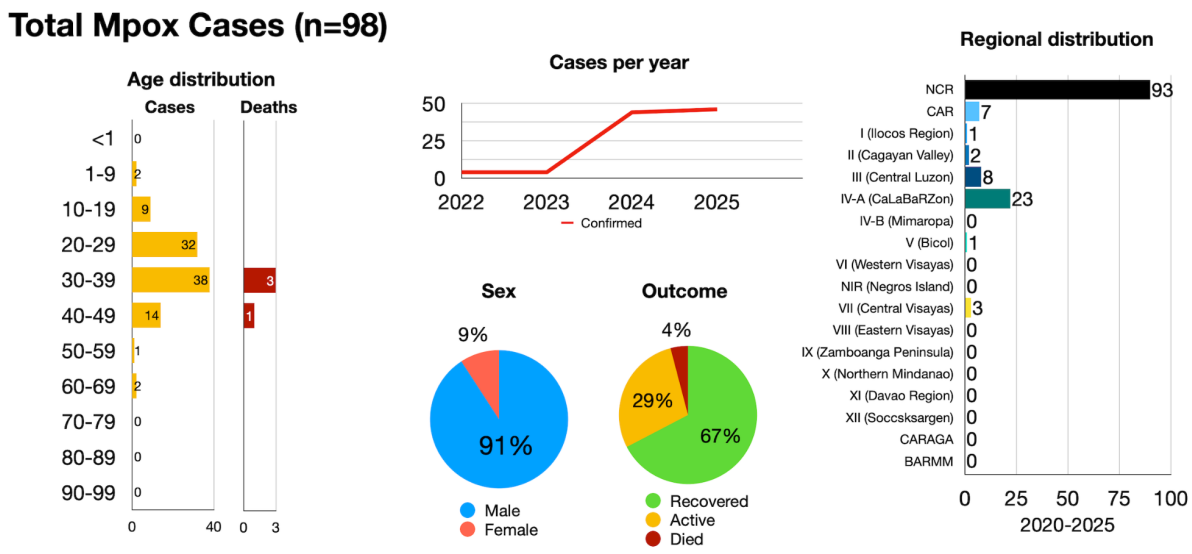


Source: Epidemiology Bureau, Department of Health (as of 02 May 2025)
COVID-19 case data from TanodKontraCOVID (TKC)
Data on long COVID is currently unavailable.
Reported deaths are for surveillance only and are unofficial. The official source of mortality data is the Philippine Statistics Authority (PSA)

Figure 3. Epidemiology of COVID-19 in the Philippines in 2024.

Mpox

An emerging health concern at present is mpox which was initially reported by the WHO in 2022.[9] After two years, in August 2024, WHO declared mpox outbreak as a public health emergency of international concern.[10] They reported the emergence of a new clade of mpox with a rapid spread in eastern Democratic Republic in Congo and with reports from several neighboring countries. The Philippines is not spared—as of May 2,2025, the Department of Health (DOH) Epidemiology Bureau has recorded 98 confirmed cases of mpox since 2022 and the resurgence of local transmission in early 2024. Majority of cases occur in males (~90%) between 20 to 40 years old. Circulating mpox virus in the Philippines belongs to Clade IIb, which is associated with milder clinical manifestations and lower case fatality rates (CFR). Most cases are self-limiting and resolve within 2 to 4 weeks without hospitalization.[11,12]



Source: Epidemiology Bureau, Department of Health (as of 02 May 2025)
Philippine Integrated Disease Surveillance and Response (PIDSR) Line-list - Event-based Surveillance and Response (ESR) and Case-based Surveillance (CbSS) Mpox Database
Data includes only cases of Mpox from 2022 to 2025. Reported deaths are unofficial and are used for surveillance purposes only.
The official source of mortality data is the Philippine Statistics Authority (PSA)

Figure 4. Epidemiology of Mpox in the Philippines from 2022 to 2025 (as of May 2, 2025).

While rare, human infection with avian influenza virus can be a starting point for future pandemic. The main risk factor for avian influenza in humans is exposure to infected live or dead poultry or contaminated environments such as live bird markets.[13] Avian influenza has a CFR of 54.7%, with no new cases reported to WHO in the Western Pacific Region as of January 2024.[14] In the Philippines, the Bureau of Animal Industry is reporting outbreaks of avian influenza A(H5N1) in some poultry farms. While there is no current report of human avian influenza, these situations are high-risk settings for potential infections.

Overall, the real threat of EREIDs like pertussis, leptospirosis, COVID-19, mpox, and avian influenza stresses the importance of standardizing and regularly updating the approach to disease diagnosis, management and prevention.

Chapter 2. Objective, Scope, Target Population, and Target Users

2.1. Objectives

The CPG for EREIDs aims to provide evidence-based recommendations to healthcare professionals, policymakers, and public health officials regarding the diagnosis, treatment, and prevention of selected EREIDs.

The following were the specific objectives of the CPG:

1. To identify priority EREIDs as targets of the CPG based on disease burden, variation in practice, relevance and emerging health threats;
2. To identify priority clinical questions related to the diagnosis, management and prevention of selected EREIDs;
3. To review the literature and summarize the available evidence regarding the diagnosis, management and prevention of priority EREIDs;
4. To provide up-to-date, evidence-based recommendations for the diagnosis, clinical management and prevention of selected EREIDs in the Philippines.

2.2. Scope

This CPG covers selected EREIDs that have been identified as priority topics based on disease burden, economic burden, urgency, clinical practice variation, and gaps in health care delivery, namely: COVID-19, leptospirosis, pertussis, avian influenza, and mpox. It is not an exhaustive guide for managing all EREIDs; rather it offers recommendations in selected clinical questions where decision-making either differs in clinical practices or lacks clarity.

2.3. Target Population

Most of the recommendations are intended for the general population with some questions focused on pediatric population (i.e., on MIS-C, leptospirosis prophylaxis, pertussis vaccines) and pregnant women (i.e., leptospirosis prophylaxis), although subgroup considerations are identified and stated when applicable.

2.4. Target Users and Institutions

The CPG for EREIDs is intended to assist health care workers (e.g., physicians, nurses, paramedical staff, etc.) in the diagnosis, management and prevention of selected EREIDs like pertussis, leptospirosis, COVID-19 infection, mpox and avian influenza among children and adult populations. Primary care physicians and specialists alike may benefit from the CPG which should guide them in the management of their patients. Medical and paramedical trainees will learn up-to-date recommendations regarding EREID diagnosis, management and prevention. Medical organizations as well as the DOH as policy-making bodies may utilize the CPG in crafting local policies that address the negative impact of EREIDs.

While this CPG reflects the best available evidence, adhering to the recommendations does not always guarantee the best outcome. These guidelines are intended to support, not replace clinical judgment in making treatment decisions, while also taking into consideration patients' personal values and individual circumstances. Guidelines are not mandates and should not be interpreted as legal standards of care.

Chapter 3. Guideline Development Methodology

3.1. Organization of the Process

Convening the Steering Committee, Technical Working Group, Guideline Panel, and Conflict of Interest (COI) Review Committee

The Guideline Development Group on Emerging and Reemerging Infectious Diseases (GDG-EREID) is composed of the Steering Committee (SC), Technical Working Group and Evidence Review Experts (TWG/EREs), the Guideline Panel (GP), and the external Conflict of Interest Review Committee (COIRC). The composition of the group—a multidisciplinary team of clinicians, researchers, epidemiologists, public health experts, and patient representatives—ensured a collaborative and coordinated effort in guideline development. All members of the GDG underwent conflict of interest (COI) review and identified potential COIs were managed accordingly. Members of GDG-EREID are listed in **Appendix A**.

Managing Conflicts of Interest

All members of the GDG-EREID completed and submitted their respective COI declaration forms and curriculum vitae to the COIRC whose members are outside the GDG. Chapter 5 shows the COIs, if any, of members of the GDG-EREID. Identified conflicts were reviewed and appropriately managed in accordance with established procedures to ensure the integrity and objectivity of the guideline development process. Potential COIs were managed as follows:

A - Allowed to participate without constraints
B - Allowed to participate but required to broadcast intellectual or non-financial COIs; such COIs would also be declared in writing in the CPG document
C - Cannot vote, but may still participate by sharing their expertise with the group
D - Disallowed to participate in the entire CPG development process or to particular questions addressed by it

Prioritizing the Clinical Questions

The following priority EREID topics were initially identified: COVID-19, Leptospirosis, Pertussis, Dengue, Avian influenza and Chikungunya. These topics were then rated based on the following criteria: disease burden (30%), economic burden (20%), urgency (20%), clinical practice variation (20%), and gaps in health care delivery (10%). The rating by the SC members was then ranked to come up with the top 5 priority topics as follows: 1 - COVID-19, 2 - Leptospirosis, 3 - Pertussis, 4 - Avian influenza, and 5 - Chikungunya versus Dengue clinical diagnosis. Dengue was removed from the initial list since a CPG for dengue was just released in 2023.[15] A new development regarding dengue vaccine will be suggested in the next Periodic Health Exam Immunization CPG update.

The above topics were presented to stakeholders representing different medical, paramedical, and patient organizations for comments and suggestions as well as topic finalization. After discussion on the initial priority topics, the steering committee and the representatives of stakeholders has decided on a new set of priority topics as follows: **COVID-19 infection**, **leptospirosis**, **pertussis**, **mpox**, and **avian influenza**.

Clinical questions were initially identified for each chosen priority topic during the first SC meeting. The clinical questions were refined following the Population, Intervention, Comparison, and Outcome (PICO) framework to guide the literature search and evidence appraisal. The drafts of the refined clinical questions were presented to the GP as stakeholders for comments, suggestions and prioritization. Priority guideline questions were also given

by the DOH Disease Prevention and Control Bureau and subsequently discussed by the SC. Likewise, the GP members were asked to identify the critical outcomes which they consider to be important for decision-making for each question. The SC with the help of the Technical Leads then finalized the guideline questions as shown below.

Topic 1: COVID-19

GUIDELINE QUESTION 1: Should we provide rehabilitative interventions for persons with long 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

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

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)
Comparison	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

Topic 2 : Leptospirosis

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
Comparison	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)

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
Comparison	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

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
Comparison	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

Topic 3: Pertussis

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
Comparison	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

Topic 4: Avian influenza

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
Comparison	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
Subgroups (if any)	By timing of testing
Methods	Observational studies (diagnostic cross-sectional, cohort); diagnostic RCTs

Topic 5: Mpox

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)
Comparison	No quarantine
Outcomes	Incidence of mpox
Subgroups (if any)	Not applicable
Methods	Observational studies

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
Comparison	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

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)
Comparison	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

3.2. Evidence Summaries

The GRADE-ADOLOPMENT method was applied in this CPG, integrating the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach with aspects of guideline adaptation, adoption, and de novo development.[16] It was used to assess the quality of evidence that supports the recommendations in the existing guidelines.[17] These existing recommendations were modified as needed to ensure their suitability for the new context, considering factors such as current local disease burden, patient values and preferences, and resource availability. When existing guidelines were deemed inadequate, new recommendations were developed *de novo* using the GRADE methodology to address the questions listed above.

Search Methods and Strategies

The EREID CPG development process involved a systematic and evidence-based approach to ensure that the recommendations are reliable, relevant, and effective. All published local or international CPGs related to the identified EREID topics were searched from various electronic databases like PubMed, Guidelines International Network (G-I-N), National Guideline Clearinghouse, and organization-specific repositories. Two reviewers screened and selected the studies based on the inclusion and exclusion criteria. Guideline quality was assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE-II) tool,[18] and guidelines that scored high on assessment were selected.

A comprehensive and systematic literature search in international CPG databases (e.g., Guidelines International Network, United Kingdom National Institute for Health and Care Excellence), local CPG databases (e.g., DOH website and HERDIN), websites of international and local specialty societies, and electronic bibliographic databases (e.g., MEDLINE, CENTRAL, EMBASE, Clinicaltrials.gov, Google Scholar) was done using a combination of keywords and free-text search related to the PICO for each guideline question. High-quality and up-to-date (i.e., search date done within the last 2 years) systematic reviews found were used as the body of evidence to inform guideline recommendations and updated as necessary.

Inclusion and Exclusion Criteria

Criteria for including or excluding studies were adapted for each guideline question to ensure that the evidence is relevant to the guideline question. The criteria for each guideline question are available in **Appendix B**. RCTs or systematic reviews of RCTs were the preferred study design for questions on interventions. If RCTs were not available, NRSIs such as observational cohort studies and quasi-randomized trials were included. For diagnosis-related questions, cohort or cross-sectional designs were primarily sought.

Data Extraction

Summaries of the evidence underpinning each recommendation were extracted including the details on study designs, sample sizes, results, and limitations. The context and rationale provided in the original guidelines for each recommendation were documented and recorded, taking notes on the assumptions, value judgments, or contextual factors that were considered.

For guideline questions that required a *de novo* systematic review process, data regarding the study participants, design, interventions, comparators, primary and secondary outcomes, and report characteristics were extracted. Raw data used to obtain effect estimates were extracted from each study whenever possible.

Synthesis of Evidence

Before commencing any *de novo* systematic literature search, the evidence base used in all existing local and foreign CPGs that have been appraised to be of 'good quality' were reviewed and updated. Evidence reviews were done by EREs who identified and independently critically appraised primary studies and systematic reviews. One primary ERE was assigned per guideline question, although other independent reviewers (the Technical Lead, Assistant Technical Lead, or another evidence review expert) were involved in screening full-text articles for potential inclusion in the review. In the absence of published systematic reviews, meta-analyses were done by pooling the data of several related studies. Pooled effect estimates were calculated, as applicable, using RevMan 5.0 or R Version 4.4.1. Evidence summaries that discuss the balance of benefits and harms of each intervention or diagnostic test were prepared by the TWG and distributed to the GP to guide their decision-making process in formulating recommendations.

Study Quality Assessment and Certainty of Evidence

Critical appraisal and risk of bias assessments of the gathered studies were done by at least two EREs. The Cochrane Risk of Bias tool 2 (for intervention studies),[19] Newcastle Ottawa Scale[20] or ROBINS-I tool[21] (for observational studies), and QUADAS-2 (for diagnostic accuracy studies)[22] were used to assess the risk of bias. On the other hand, the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system was used to assess the overall certainty of the evidence regarding the intervention effects.[23] The overall certainty of the evidence was determined based on the *lowest* certainty rating of the top seven critical and important outcomes. The rating of importance of outcomes into critical, important, or relevant was decided on by the multi-sectoral GP prior to the completion of the evidence synthesis.

The initial rating of certainty of evidence was 'high' for RCTs, and 'low' for non-randomized studies of interventions (NSRIs) which included observational studies, case series, and case reports. For RCTs with issues such as high risk of bias, inconsistency, indirectness, imprecision, and publication bias, the rating for certainty of evidence was downgraded. NSRIs and observational studies with large magnitude of effect, evidence of a dose-response gradient, or if plausible confounding would reduce a demonstrated effect were upgraded. For any discrepancies in the assessment, these were resolved through discussion until consensus was reached.

3.3. Formulation of the Recommendations

Evidence to Decision Frameworks

The gathered evidence was translated into actionable recommendations. The strength and direction of recommendations were graded using the GRADE approach, and the Evidence to Decision Framework considered factors such as quality of evidence, balance of benefits and harms, patient values and preferences, resource implications, feasibility, acceptability, and equity. Cost estimates and cost-effectiveness data were based only cursory searches from publicly available sources (e.g., websites of drug stores, 2024 Philippine Drug Price Reference Index [DPRI], or personal communication or personal knowledge by the evidence reviewers or guideline panelists). Due to time and resource constraints, formal costing studies or economic evaluation were not done. Prior to the *en banc* meeting, each GP answered an ETD Framework for each guideline question to obtain their judgments for each ETD domain. Responses from all GPs were summarized and the modal response for each item was identified for each. The Evidence to Decision frameworks for each question are available as **Appendix C**.

Consensus Process

The evidence summaries were sent to members of the GP. An *en banc* GP meeting was held to finalize the recommendations, moderated by an experienced facilitator. During the meeting, an assigned evidence reviewer presented the evidence summary for each question. Panelists classified to have an "A", "B", or "C" COI rating were allowed to ask for clarification regarding the evidence presented and other issues related to the question. After discussing among themselves, the facilitator asked the GP members classified to have an "A" or "B" COI rating to vote on the direction (for or against or abstain), the strength of recommendation (weak or strong), and the wording of the recommendation.

A ***strong*** recommendation was made when benefits clearly outweighed harms; a ***weak*** recommendation reflected uncertainty due to limited evidence, unclear trade-offs, or when expected benefits may be limited or vary based on patient values, preferences, and clinical context. Standardized language (e.g., "We recommend" for *strong*, "We suggest" for *weak*) were used. *Weak* recommendations reflect uncertainty in the evidence, not a lack of importance. While these recommendations may warrant flexibility in implementation, they still support action and should not be interpreted as a reason to delay policy, reimbursement, or coverage decisions in areas of urgent public health.

A consensus was defined by at least 75% agreement among the voting GP members. When consensus was not reached, each panelist was asked to explain the rationale behind their vote, then another round of voting commenced. At most 3 rounds of voting were done to reach a consensus. In cases where there was no evidence identified but the intervention would likely result in benefit more than harm, a good practice statement was formulated. A Delphi approach was used to achieve consensus regarding one Recommendation 11.1, where the strength of the recommendation had to be updated due to the publication of results of an ongoing RCT.

3.4. Planning for Dissemination and Implementation

A comprehensive strategy for the effective introduction of the practice guidelines will be developed. To tailor the message to the appropriate stakeholders and target audience, various channels will be considered for dissemination. Upon approval, the CPG will be published in the DOH Compendium of CPGs website (https://doh.gov.ph/dpcb/doh-approved-cpg/) and in the official websites of the An abridged manuscript of the CPG will be published in the Acta Medica Philippina.

3.5. External Review

Two methods for external review were used: CPG appraisal using AGREE-REX instrument and stakeholder feedback. Three external reviewers were invited to evaluate the methodological rigor of the guideline development process, clarity of presentation, acceptability, and feasibility of the recommendations. The AGREE-REX tool consists of 9 items focused on the following: guideline purpose, local applicability, evidence quality, and values and preferences of patients or populations, target users, and decision-makers.[24] The external reviewers included guideline advocates, clinical experts, DOH, and other relevant stakeholders. Feedback from external reviewers were summarized and key areas for improvement were identified **(Appendix D)**. The CPG was then revised by the Steering Committee, Technical Writer, and Technical Leads by incorporating the feedback from the external reviewers. After the external review, the CPG was submitted to the DOH Clearing House for review and approval.

Once the CPG is published and uploaded on the DOH website and medical society websites, comments and suggestions from the users will be gathered. The CPG will then be revised, if necessary, by incorporating the feedback from the stakeholders.

Table 2. Summary of external review results based on AGREE-REX tool.

AGREE-REX Item	Rating[a]			
	Reviewer 1	Reviewer 2	Reviewer 3	Average Rating
Item 1. Evidence	2	6	6	4.7
Item 2. Applicability to target users	6	6	5	5.7
Item 3. Applicability to patients/ populations	6	6	6	6
Item 4. Values and preferences of target users	6	5	4	5
Item 5. Values and preferences of patients/populations	5	4	6	5
Item 6. Values and preferences of policy/decision-makers	6	6	5	5.7
Item 7. Values and preferences of guideline developers	6	7	7	6.7
Item 8. Purpose	6	7	5	6
Item 9. Local application and adoption	6	5	5	5.3
Overall				
I would recommend these guideline recommendations for use in the appropriate context.	Yes	Yes, with modifications	Yes	
I would recommend these guidelines for use in my context.	Yes	Yes, with modifications	Yes	

a Score of 1 = Strongly disagree; 7 = Strongly agree

3.6. Editorial Independence

The development of this CPG was funded by DOH Philippines through the Institute of Clinical Epidemiology of the National Institutes of Health, University of the Philippines Manila. While the DOH has identified some priority questions (e.g., questions on COVID 2024-2025 vaccines – Q3, acellular pertussis vaccine – Q7), it had no influence on the evidence synthesis, formulation of recommendations, or conclusions of this guideline. The views expressed herein are solely those of the guideline development group and do not necessarily represent the official policies or positions of the DOH as the funding agency.

Chapter 4. Recommendation and Evidence Summaries

Guideline Question 1.
Rehabilitation for Long Coronavirus Disease (COVID)

Should we provide rehabilitative interventions for persons with long COVID symptoms?

Recommendation 1.
We suggest the use of rehabilitative interventions in adults with long COVID symptoms.

Certainty of evidence:	Very low
Strength of recommendation:	Weak

Guideline Panel Considerations

Despite the overall very low certainty of evidence, the GP issued a weak recommendation to offer rehabilitative interventions to adults with long COVID symptoms.

Select interventions with moderate-certainty evidence, such as intermittent aerobic exercise, online CBT, and comprehensive physical and mental rehabilitation programs, likely provide meaningful benefits for fatigue reduction, improvements in physical function, and enhanced quality of life. The risks associated with these interventions are generally low. Rehabilitation aligns with patient values and preferences, addressing the most frequently reported long COVID symptoms, including fatigue, exercise intolerance, and mental health concerns. Patients are likely to desire access to interventions that may improve these outcomes, even in the context of evidence limitations.

The panel recognized significant implementation challenges, particularly regarding equitable access and limited evidence for the pediatric population. Availability of structured rehabilitation services is limited in many settings, especially in rural or resource-constrained areas, and cost and workforce limitations may restrict widespread uptake. The panel emphasized that rehabilitation strategies should be adapted whenever available.

Key Findings

- This summary includes findings from 13 non-pharmacological studies involving 1,682 participants with post-COVID-19 conditions. The studies were methodologically diverse (5 RCTs, 3 double-blind RCTs, 2 single-blind RCTs, 1 open-label RCT, 2 pragmatic trials) and generally limited by small sample sizes and varying risks of bias. The certainty of evidence ranged from very low to moderate. Interventions were categorized into four domains:
    - exercise-based and respiratory therapies (e.g., aerobic training, breathing techniques),
    - behavioral interventions (e.g., online cognitive behavioral therapy (CBT), telerehabilitation, amygdala and insula retraining (AIR)),
    - medical device-based approaches (e.g., hyperbaric oxygen therapy (HBOT), transcranial direct current stimulation (TDCS), photobiomodulation (PBM)), and
    - comprehensive rehabilitation programs integrating both physical and mental health strategies.

- Interventions with demonstrated benefit for post-COVID-19 conditions varied in certainty. Moderate-certainty evidence supports intermittent aerobic exercise, online CBT, and comprehensive physical and mental rehabilitation, all of which likely improve physical function, reduce fatigue, and enhance quality of life. Low-certainty evidence suggests that physiotherapy (PT) with multicomponent exercise, aerobic and strength training, inspiratory muscle training (IMT), breathing techniques, and acupuncture (when combined with rehabilitation) may offer additional benefits, particularly for dyspnea, pulmonary outcomes, and overall function, though findings are less consistent and impacted by higher dropout rates or limited effect clarity.
- Interventions with little to no demonstrated benefit were supported by low to very low certainty evidence, indicating uncertain or minimal effects. Telerehabilitation delivered *via* mobile apps showed limited or no sustained impact on fatigue or functional outcomes. AIR offered minimal or uncertain benefit for fatigue reduction and self-management. HBOT yielded mixed results, with possible cognitive improvements but unclear effects on fatigue and overall function. TDCS may influence fatigue and mood, though its impact on physical function remains uncertain. PBM showed minimal observed benefit for post-COVID-19 symptoms.

Background

Long COVID affects a significant portion of the global population, with at least 65 million people suffering from this condition and approximately 5% of the general population reporting persistent symptoms—three-quarters of whom experience these symptoms for more than a year.[25,26] A retrospective study at the Philippine General Hospital found that among 171 discharged COVID-19 patients, 26% reported persistent symptoms at three months, primarily dyspnea, fatigue, and cough. While 88% remained fully independent and did not require special care, only 39.8% had returned to their baseline work, indicating ongoing functional limitations for a significant portion.[27] In another cohort study involving adults residing in Cebu, NCR, Central Luzon, and West Visayas and who tested positive for SARS-CoV-2 infection, at least 68% reported long COVID symptoms. General and neuropsychiatric symptoms were most common, including intermittent fatigue, headache, and brain fog.[28]

Effective rehabilitation interventions (i.e., exercise-based and respiratory therapies, cognitive and digital rehabilitations, comprehensive rehabilitation programs) are critical for enhancing quality of life by improving functional capacity, reducing fatigue, ameliorating mental health outcomes, and increasing independence in activities of daily living.[29,30] Given the substantial economic implications of long COVID, including reduced work capacity and increased healthcare utilization, targeted rehabilitation strategies may help reduce sick leave rates, improve functional levels, and facilitate return to work.[25]

Evidence-based guidance on rehabilitation is also essential for informing clinical practice by helping clinicians make informed decisions, prevent the use of unproven or harmful treatments, and ensure the safety of exercise-based interventions through appropriate pacing and intensity adjustments to mitigate risks such as post-exertional malaise.[25,26] Furthermore, understanding effective rehabilitative interventions is crucial for tailoring treatments to specific symptom clusters and the needs of vulnerable populations, such as older adults, thereby optimizing rehabilitation programs and advancing research to identify gaps, guide future studies, and contribute to the development of standardized protocols with far-reaching implications for patient care, healthcare policy, and clinical practice.

Summary of the Evidence

Characteristics of included studies

We included 1 living systematic review (Zeraatkar 2024) that comprehensively covers randomized controlled trials on rehabilitative interventions for long COVID.[30] This review was selected as the sole source due to its rigorous methodology (based on AMSTAR-2 tool), up-to-date synthesis of evidence, and ongoing updates, making the

inclusion of additional systematic reviews unnecessary and potentially redundant. Most studies in the living systematic review enrolled adults (≥18 years) diagnosed with long COVID, defined by persistent symptoms at least 3 months post-infection. Some studies targeted specific subgroups, such as patients with post-COVID-19 syndrome, older adults with sarcopenia, and individuals experiencing fatigue. Sample sizes varied, ranging from 70 participants to 110. Some studies focused on specific subpopulations, such as older adults, while others included broader long COVID populations.

This review examined a diverse set of rehabilitative interventions for long COVID, encompassing variations in study populations, intervention types, comparators, and measured outcomes. The frequency, duration, and intensity of interventions also varied. The rehabilitative interventions were divided into 4 types, as shown in Table 3.

Table 3. Types of rehabilitative interventions for long COVID.

Physical Activity and Rehabilitation (6 RCTs)	Behavioral Interventions (3 RCTs)	Medical Device and Technologies (3 RCTs)	Combined Treatment (Physical and Mental Rehabilitation) (1 RCT)
a. Intermittent aerobic exercise b. Multicomponent exercise with PT c. Low- vs. high-intensity aerobic and strength training d. In-patient rehabilitation combined with acupuncture e. IMT f. PT with active cycle of breathing techniques (ACBT) g. Structured physical activity programs vs. usual care or education	a. Online CBT – "Fit after COVID" b. Educational mobile application – ReCOVery app c. AIR	a. HBOT b. High-definition TDCS c. PBM	a. Supervised group exercise sessions b. Psychological support sessions c. Motivation training d. Fear avoidance strategies e. Emotion management f. Fatigue management g. Stress and anxiety management

The comparators varied across studies, with some trials using placebo or sham interventions, including sham treatments for HBOT, TCDS, and cognitive retraining. Others compared interventions to standard care or usual rehabilitation programs, such as telerehabilitation against routine care or standard pulmonary rehabilitation. Several studies compared different non-drug interventions, such as intermittent versus continuous aerobic exercise and low- versus high-intensity resistance training.

The studies assessed a range of physical, respiratory, cognitive, and quality-of-life outcomes. Physical function was evaluated through six-minute walk tests and functional exercise capacity assessments. Respiratory function was measured using spirometry and inspiratory pressure testing (5). Fatigue and mental health were assessed using validated fatigue scales and cognitive function tests. Patient-reported quality-of-life measures were also used. Risks like post-exertional symptom exacerbation (PESE) were not assessed as outcomes of interest in the included trials.

Efficacy outcomes: physical activity and rehabilitation (6 RCTs, N = 611)

Among physical activity and rehabilitation interventions (6 RCTs, N = 611) (Table 4), intermittent aerobic exercise demonstrated the strongest evidence, with moderate-certainty support for improving physical function. In contrast, other non-pharmacological interventions—such as multicomponent exercise, IMT, and acupuncture—

may provide benefits for dyspnea and physical function; however, these findings are supported by low or very low-certainty evidence. Furthermore, the effects of these interventions on mental health and quality of life remain inconclusive due to methodological limitations.

- Intermittent aerobic exercise performed 3 to 5 times per week for 4 to 6 weeks probably improves physical function compared to continuous aerobic exercise, supported by moderate-certainty evidence, though it shows no clear effect on mental health.[31]
- Physiotherapist-supervised multicomponent exercise program, delivered twice weekly for 60 minutes over 10 weeks, also may improve physical function and reduce dyspnea, though certainty is low due to small sample sizes; its effect on mental health is unclear.[32]
- IMT may reduce dyspnea, while low- versus high-intensity aerobic and strength training conducted four days per week for eight weeks in men with long COVID and sarcopenia suggests possible quality of life improvements—both supported by low-certainty evidence.[33]
- Inpatient rehabilitation combined with acupuncture showed potential dyspnea improvement, but evidence is low certainty due to risk of bias.[34]
- ACBT plus BT yielded a large apparent fatigue reduction, yet the evidence is very uncertain.[35]

Table 4. Summary of findings: physical activity and rehabilitation for long COVID.

Outcomes	Multicomponent exercise of progressively increasing intensity[a] vs. standard PT	Intermittent exercise vs. continuous exercise[b]	Low vs. high intensity aerobic exercise and strength training[c]	Inspiratory muscle training vs. usual care[d]	PT + Active cycle of breathing technique vs. PT alone[e]	In-patient rehabilitation + PT + acupuncture vs. in-patient rehabilitation + PT only[f]
	1 RCT[32] (N = 60)	**1 RCT[31] (N = 110)**	**1 RCT[36] (N = 73)**	**1 RCT[33] (N = 148)**	**1 RCT[35] (N = 60)**	**1 RCT[34] (N = 160)**
Fatigue assessed *via*: Fatigue Assessment Scale-10 (range 10–50; lower = better)					**MD -9.9 (-11.2–-8.8)** 12 wks	
Physical function assessed *via*: SF-36 physical component score (range 0–100; higher = better)	**MD 6.9 (2.7–11.2)** 12.8 wks	**MD 3.8 (1.1 to 6.5)** 5 wks				
Cognitive function						
Mental health assessed *via*: SF-36 mental component score (range 0–100; higher = better)	**MD 2.1 (-3.5–7.6)** 12.8 wks	**MD 0 (-3.7–3.7)** 5 wks				
Quality of life or wellbeing assessed *via*: SarQol score[36] (range 0–100; higher = better)			**MD 10.4 (10.0–10.8)** 8 & 24 wks	**MD -1.3 (-5.9–3.3)** 8 wks		

Outcomes	Multicomponent exercise of progressively increasing intensity[a] vs. standard PT	Intermittent exercise vs. continuous exercise[b]	Low vs. high intensity aerobic exercise and strength training[c]	Inspiratory muscle training vs. usual care[d]	PT + Active cycle of breathing technique vs. PT alone[e]	In-patient rehabilitation + PT + acupuncture vs. in-patient rehabilitation + PT only[f]
	1 RCT[32] (N = 60)	**1 RCT[31] (N = 110)**	**1 RCT[36] (N = 73)**	**1 RCT[33] (N = 148)**	**1 RCT[35] (N = 60)**	**1 RCT[34] (N = 160)**
OR King's Brief Interstitial Lung Disease total score[33] (range 0–100; higher = better						
Dyspnea assessed *via*: Modified Medical Research Council Dyspnea Scale[32,34] (range 0–4; lower = better) OR Transition Dyspnea Index[33] (range -9–9; higher = better)	**MD -0.8 (-1.2–-0.3)** 13 wks			**MD 1.1 (0.4–1.7)** 8 wks		**MD -0.6 (-0.7–-0.5)** 1.7 wks

GRADE ratings and interpretation				
	High certainty	Definitely more effective	Definitely worse	Definitely no different
	Moderate certainty	Probably more effective	Probably worse	Probably no different
	Low certainty	May be more effective	May be worse	May be no different
	Very low certainty	Very uncertain		

a 2 × 60 min/week for 10 weeks by trained PT vs. usual care 2 × 30 min/week for 10 weeks
b 3–5 sessions/week; 18 min 4-6 weeks as either continuous training (CT) at 50% of maximal workload or as interval training (IT; load = 60%, relief = 30%)
c 30 minutes/session, 1 session/day, 4 days/week for 8 weeks
d 8-week IMT or a "usual care" waitlist control arm
e Thoracic expansion exercises and forced expiration technique 20-30 seconds, 3-4x vs Active limb exercises followed by progressive muscle strengthening 3 sets of 8-15 reps, 10-45 min sets, 1-3x / week
f In-patient rehabilitation (respiratory gymnastics, massage, myorelaxation, physical therapy, speleotherapy, exercise equipment, aerosol therapy, oxygen cocktail, magnetotherapy, amplipulse, ultrawave frequencies, ultrasound therapy, ultraviolet irradiation, shungite therapy, inhalation, and outdoor walks) vs. acupuncture 7-10 treatment sessions conducted every day (full-body dry acupuncture treatment, in which 10 points were applied: 9 basic points, and 1 point depending on the specific complaint (e.g., shortness of breath, cough, cognitive impairment, increased blood pressure, joint pain and headache)

Efficacy outcomes: behavioral interventions (3 RCTs, N = 243)

The 17-week Fit after COVID online CBT program[37] (N = 114), compared to usual care or waitlist, likely reduces fatigue and improves cognitive function, supported by moderate-certainty evidence. It may also increase the likelihood of fatigue recovery, though this is less certain. Effects on physical function are unclear. Other interventions, such as the ReCOVery telerehabilitation app[38] (N = 87) and the AIR program[39] (N = 42), compared to usual care or minimal intervention, show no clear or consistent benefits for fatigue, cognition, physical function, or mental health, with only low or very low-certainty evidence. Overall, only the "Fit after COVID CBT" demonstrates probable benefits, mainly for fatigue and cognition,[37] while other interventions have inconclusive or uncertain effects. Table 5 summarizes the findings for behavioral interventions.

Table 5. Summary of findings: behavioral interventions for long COVID.

Outcomes	Online CBT program "fit after COVID"[a] vs. usual care *(no structured CBT program)*	Telerehab mobile app (ReCOVery)[b] vs. usual care *(no app)*	AIR[c] vs. education related to self-management
	1 RCT[37] (N = 114)	**1 RCT[38] (N = 87)**	**1 RCT[39] (N = 42)**
Fatigue assessed *via*: CIS-fatigue subscale <35[37] (range 8–56; lower = better) OR Multidimensional Fatigue Inventory-20[39] (range 20–100; lower = better)	**RR 2.4[d] (1.5–4.0)** 24 wks		**MD -1.5 (-3–0.04)** 12 wks
Physical function assessed *via*: SF-36 physical component score (range 0–100; higher = better)	**MD 4.9 (-1.9–11.7)** 24 wks	**MD -3.5 (-9.1–2.2)** 24 wks	
Cognitive function assessed *via*: Montreal Cognitive Assessment (range 0–30; higher = better)		**MD 0.6 (-0.9–2.1)** 24 wks	
Mental health assessed *via*: CIS concentration subscale[37] (range 5–35; lower = better) OR SF-36 mental component score[38] (range 0–100; higher = better)	**MD -5.2 (-8.0–-2.4)** 24 wks	**MD -1.9 (-5.4–9.1)** 24 wks	
Quality of life or wellbeing			
Dyspnea			

GRADE ratings and interpretation			
High certainty	Definitely more effective	Definitely worse	Definitely no different
Moderate certainty	Probably more effective	Probably worse	Probably no different
Low certainty	May be more effective	May be worse	May be no different
Very low certainty	Very uncertain		

a 17 weeks, by trained psychologists
b Mediterranean diet, 7-8h sleep, respiratory + breathing exercise video tutorials, cognitive stimulation
c Mindfulness meditation, alternate nostril breathing, lifestyle therapy
d Higher RR indicates better outcome

Efficacy outcomes: medical devices and technologies (3 RCTs, N = 243)

TDCS combined with PT and education[40] (RCT, N = 70) may reduce fatigue and improve cognitive fatigue, anxiety, and quality of life at five weeks, supported by low-certainty evidence due to imprecision. PBM[41] (RCT, N = 100) showed a small fatigue improvement and marginal physical function benefit but concerns about trial integrity lower confidence despite moderate-certainty evidence for fatigue. HBOT versus placebo[42] (RCT, N = 73) showed no clear physical function benefit, slight cognitive improvement, and modest mental health gains, all supported by low-certainty evidence limited by imprecision and bias. Overall, medical devices and technologies may help long COVID symptoms, especially fatigue and cognition, but evidence is limited by small samples, methodological issues, and low to moderate certainty (Table 6).

Table 6. Summary of findings: medical devices and technologies for long COVID.

Outcomes	HBOT vs. placebo 1 RCT[42] (N = 73)	TDCS vs. PT + education related to self-management 1 RCT[40] (N = 70)	PBM vs. placebo 1 RCT[41] (N = 100)
Fatigue assessed *via*: No of subjects with 5 pt reduction in Modified Fatigue Impact Scale score[40] OR Fatigue Severity Scale[41] (range 1–7; lower = better)		**RR 1.7[a]** **(1.1–2.5)** 5 wks	**MD -0.3** **(-0.4–-0.2)** 4 wks
Physical function assessed *via*: Brief Symptom Inventory-18[42] (range 0–72; lower = better) OR Katz Index of Independence in Tasks of Everyday Living[41] (range 0-6; higher = better)	**MD -5.2** **(-14.1–3.7)** 10 wks		**MD 0.3** **(0–0.6)** 4 wks
Cognitive function assessed *via*: NeuroTrax Computerized Cognitive Testing Battery Global Score[42] (mean 100 SD 15; higher = better) OR Modified Fatigue Impact Scale – cognitive fatigue score[40] (range 0–40; lower = better)	**MD 3.4** **(0.3–6.5)** 10 wks	**MD -9.3** **(-13.1–-5.5)** 5 wks	
Mental health assessed *via*: Brief Symptom Inventory-18[42] (range 0–72; lower = better) OR Hamilton Anxiety Rating Scale score[40] (range 0–56; lower = better)	**MD -7.1** **(-12.2–-2.0)** 10 wks	**MD -4.9** **(-7.5–-2.3)** 5 wks	
Quality of life or wellbeing WHO QOL questionnaire (range 0–100; higher = better)		**MD 14.8** **(8.9–20.7)** 5 wks	
Dyspnea			

GRADE ratings and interpretation				
	High certainty	Definitely more effective	Definitely worse	Definitely no different
	Moderate certainty	Probably more effective	Probably worse	Probably no different
	Low certainty	May be more effective	May be worse	May be no different
	Very low certainty	Very uncertain		

a Higher RR indicates better outcome

Efficacy outcomes: combination intervention (1 RCT, N = 585)

The REGAIN trial (N = 585) evaluated a supervised, online, home-based group rehabilitation program for long COVID patients with a history of severe COVID-19, compared to usual care consisting of a single online advice session and an informational booklet.[43] At 52 weeks, the program probably improved overall recovery (RR 1.55, 95% CI 1.21–2.00), fatigue (MD -2.00), depression (MD -1.50), and quality of life (MD 0.04), supported by moderate-certainty evidence. However, no clear benefit was found for physical function (MD 0.50), anxiety (MD -1.80), or dyspnea (MD -0.50), indicating uncertain or minimal effects for these outcomes (Table 7).

Table 7. Summary of findings: combination intervention for long COVID.

Outcomes	Physical and mental health rehabilitation (REGAIN program)[a] vs. usual care[b]
	1 RCT[43] (N = 585)
Recovery / improvement Assessed *via*: No. of patients reporting "much better/somewhat better" health	**RR 1.6[c] (1.2–2.0)** 52 wks
Fatigue Assessed *via*: PROMIS Fatigue subscore (mean 50 SD 10; lower = better)	**MD -2.4 (-3.8–-1.0)** 12 wks
Physical function Assessed *via*: PROMIS Physical function subscore (mean 50 SD 10; lower = better)	**MD 0.5 (-1.0–2.0)** 52 wks
Cognitive function	
Mental health Assessed *via*: HADS anxiety subscale (range 0–21; lower = better)	**MD -1.0 (-1.98–-0.02)** 52 wks
Mental health Assessed *via*: HADS depression subscale (range 0–21; lower = better)	**MD -1.5 (-2.4–-0.6)** 52 wks
Quality of life or wellbeing Assessed *via*: PROPr score (range 0.02–1; higher = better)	**MD 0.04 (0–0.08)**
Dyspnea Assessed *via*: PROMIS Dyspnea Severity Short Form (mean 50 SD 10; lower = better)	**MD -0.5 (-2.4–1.4)** 52 wks

GRADE ratings and interpretation				
	High certainty	Definitely more effective	Definitely worse	Definitely no different
	Moderate certainty	Probably more effective	Probably worse	Probably no different
	Low certainty	May be more effective	May be worse	May be no different
	Very low certainty	Very uncertain		

a 8 wks online, home-based, supervised, group exercise and psycho support
b Single session of advice and support with trained practitioner
c Higher RR indicates better outcome

Safety outcomes

Serious adverse Events (4 RCTs, N = 869, very low certainty)

Four randomized controlled trials (N = 869) evaluated serious adverse events (SAEs) from various long COVID rehabilitation interventions—including CBT, telerehabilitation, TDCS with physiotherapy, and comprehensive rehabilitation—and found extremely low SAE rates (0% to 0.02%), with no significant differences between intervention and control groups (Table 8). Most studies did not report SAEs, except for one RCT which had 21 SAEs. Of these, only 1 SAE - characterized by syncope with vomiting 24 hours after an exercise session - was possibly related to the intervention. The rest were unrelated (e.g., hospital admission). However, the certainty of evidence is very low due to serious risk of bias, small sample sizes, and very serious imprecision; the trials also lacked reporting on non-serious or specific adverse events, making the overall safety profile uncertain.

Table 8. Summary of findings: serious adverse events in patients with long COVID.

Author	Intervention	Comparator	Follow-up	Basis (№ and type of studies, total participants)	Relative Risk (95% CI)	Certainty of the evidence
Kuut 2023	CBT	Usual Care	24 weeks	1 RCT (N = 114)	RD 0% (-3–3%)	⊕◯◯◯ Very low[a,b]
Samper-Pardo 2023	Telerehabilitation app	Usual Care	24 weeks	1 RCT (N = 100)	RD 0% (-4–4%)	⊕◯◯◯ Very low[c,d]
Santana 2023	TDCS, PT, Education related to activities of daily living	PT, Education related to self-management	5 weeks	1 RCT (N = 70)	RD 0% (-5–5%)	⊕◯◯◯ Very low[e]
McGregor 2024	Physical and mental health rehabilitation	Usual Care	52 weeks	1 RCT (N = 585)	RD 0.02% (-0.01–0.05%)	⊕◯◯◯ Very low[f,g,h]

a Concerns related to bias due to deviations from the intended intervention and measurement of outcome.
b Confidence interval includes no important effect and appreciable harm. Only one event was observed in the trial.
c Concerns related to bias due to the randomization process, deviations from the intended intervention, and measurement of outcome.
d Confidence interval includes no important effect and appreciable harm. No events reported in trial.
e Likely much too few participants to achieve prognostic balance. Confidence interval includes no important effect and appreciable harm. No events reported in trial.
f All patients experienced severe COVID-19 infection, requiring hospitalization. We opted to not rate down the certainty of evidence for indirectness because there is no current evidence that suggests the effects of the intervention may be different based on severity of the acute COVID-19 infection.
g Concerns related to bias due to deviations from the intended intervention, missing outcome data, and measurement of outcome.
h Confidence interval includes no important effect and appreciable harm. Few events observed in the trial.

Other Considerations

Costs

As shown in Table 9, HBOT is the most expensive long COVID intervention (₱2,473–₱9,627/session) and is not covered by PhilHealth. AIR programs and CBT cost ₱1,000–₱4,500/session, with additional fees for full programs or intake. TDCS with rehab ranges from ₱500–₱4,500 depending on setting and equipment needs. Physical rehabilitation strategies cost ₱300–₱1,500/session, while telerehabilitation averages ₱700 per consult. The most affordable is PBM, at ₱80–₱300/session in public hospitals and ₱700–₱1,500 in private clinics, though it requires costly equipment.

Table 9. Summary of intervention costs for long COVID.

Intervention	Cost Estimate (₱/session)	Resource Notes
AIR	₱1,000–₱4,500[44] ₱18,000–₱20,000/year (Gupta program)	Low per session; moderate one-time program fee
HBOT	₱2,473–₱9,627 (Mean: ₱6,050) (Estremera; Fixilab; Valencia)	High cost; varies by setting; not PhilHealth-covered
CBT	₱2,000–₱3,500[45] ₱1,000–₱4,500[44] ₱2,800 (intake session)[46]	Moderate to high; needs trained psychologist
PBM	₱80–₱300 (public)[47] ₱700–₱1,500 (private)[48]	High initial tech cost; session cost varies
TDCS + Rehabilitation	₱500 (public)[47] – ₱4,500 (private)[44]	High due to device, training, supervision
Exercise Training Rehabilitation	₱300–₱1,500 (The Fort Physio)	Moderate cost; includes facility, therapist, equipment
IMT	₱300–₱1,500 (The Fort Physio)	Low-cost devices; mostly unsupervised
Interval & Continuous Aerobic Training	₱300–₱1,500 (The Fort Physio)	Moderate cost; needs trained staff, ergometers

Intervention	Cost Estimate (₱/session)	Resource Notes
Intensity Aerobic + Strength Training	₱300–₱1,500 (The Fort Physio)	Moderate cost; includes equipment & therapist
Telerehabilitation App[49]	₱500–₱1,000 per teleconsultation (average: ₱700)[49]	Low digital delivery; varies with clinician support

Cost effectiveness

No local research evidence was identified.

A United Kingdom-based study evaluating a program of physical and mental health rehabilitation for post-COVID-19 patients found it to be likely cost-effective, reporting an incremental cost-effectiveness ratio (ICER) of £11,941 (₱895,575) per quality-adjusted life year (QALY) and an 84% probability of being cost-effective at a £30,000 (₱2,250,000) per QALY threshold.[50] In addition, a recent cost-utility analysis conducted in Brazil demonstrated that adding inspiratory muscle training (IMT) to pulmonary rehabilitation programs for post-COVID-19 patients was also cost-effective. The study reported an ICER of US$793.93 (₱44,460.08) per QALY, which was well below the country's cost-effectiveness threshold, indicating that targeted respiratory interventions such as IMT may represent a valuable and efficient strategy in managing long COVID symptoms.[51]

No cost-effectiveness studies were found for interval and continuous aerobic training, combined low- and high-intensity aerobic training with strength training, TDCS combined with rehabilitation, PBM, CBT, HBOT, telerehabilitation mobile applications, and AIR.

Stakeholder values, preferences and acceptability

Overall, patients with long COVID value treatments that effectively address their primary symptoms, particularly fatigue and breathlessness. They prefer personalized approaches that are tailored to their unique needs and limitations, as well as interventions that offer comprehensive care encompassing both physical and mental health. Accessibility and the ability to integrate treatment into daily routines are also critical factors, along with a clear potential for measurable improvements in quality of life and overall functioning. It is essential to recognize that patient preferences can vary depending on individual experiences and the severity of symptoms. Therefore, healthcare providers should prioritize shared decision-making to ensure that treatment plans are aligned with each patient's goals, values, and circumstances.

<u>Physical Activity and Rehabilitative Interventions</u>

Patients generally show a positive attitude towards exercise-based interventions:

- Exercise rehabilitation programs are highly acceptable to patients, with one study reporting a 97.4% completion rate for a micro choice-based rehabilitation program.[52]
- Patients value personalized exercise programs that address their specific symptoms and limitations.[52]
- Many patients report improvements in fatigue, functional levels, and exercise capacity following rehabilitation interventions.[52]
- Combined aerobic and strength training programs are appreciated for their comprehensive approach to improving both cardiorespiratory fitness and muscle strength.[52,53]

<u>Behavioral Interventions</u>

Patients recognize the importance of addressing both physical and mental health aspects:

- AIR has shown promising results, with patients reporting significant reductions in fatigue and increased energy levels.[39]
- Telerehabilitation mobile applications are appreciated for their convenience and ability to provide ongoing support, particularly in improving physical function and community social support.[38]

Medical Devices and Technology

Patients show interest in innovative treatments, though preferences vary:

- HBOT has garnered attention, with 65% of patients in one study reporting clinically relevant increases in quality of life after treatment. However, 15% experienced deterioration, indicating the need for careful patient selection and monitoring.[54]
- Transcranial direct current stimulation combined with rehabilitation has shown promise in improving physical fatigue, which is a key concern for many long COVID patients.[55]

Equity and feasibility

Long COVID affects millions globally, with many experiencing persistent symptoms like fatigue and cognitive impairment.[56] Social determinants such as income, education, race, and location significantly influence who is affected and who can access care.[57] Equity concerns span all interventions. Addressing these disparities requires multilevel strategies—strengthening primary care, designing culturally sensitive interventions, and prioritizing low-resource models. Without deliberate equity efforts, long COVID therapies risk deepening existing health gaps.[29,58]

Physical Activity and Rehabilitative Interventions

- Exercise-based rehabilitation shows clinical benefits but depends on access to facilities and professionals.[59]
- IMT may aid recovery but requires equipment and self-management skills, posing barriers for those with low health literacy or limited means.[33]

Behavioral interventions

- Digital and psychological therapies (e.g., CBT, telerehabilitation) offer flexibility but face challenges with internet access, digital literacy, and mental health support.[38,60] Even lower technology mind-body approaches like AIR have uncertain accessibility and cultural fit.

Medical devices and technologies

- High-tech options like TDCS and PBM are typically limited to high-resource settings.[61,62]

Guideline Question 2.
MIS-C Diagnosis

What clinical and laboratory parameters should alert a health practitioner to suspect multisystem inflammatory syndrome in children (MIS-C) with COVID-19?

Recommendation 2.1.
We recommend the use of the following clinical parameters to increase suspicion of multisystem inflammatory syndrome in children:

- history of COVID-19, and
- fever of at least 3 days, and
- any two of the following: gastrointestinal, cardiovascular, dermatological, conjunctivitis, respiratory symptoms

Certainty of evidence: Low
Strength of recommendation: Strong

Recommendation 2.2.
We recommend the use of any of the following laboratory parameters to increase suspicion of multisystem inflammatory syndrome in children:

- C-reactive protein (CRP), D-dimer, Erythrocyte sedimentation rate (ESR), Ferritin, N-terminal pro-B type natriuretic peptide (NT-proBNP), Troponin T

Certainty of evidence: Low
Strength of recommendation: Strong

Recommendation 2.3.
We recommend the use of the following clinical parameters to increase suspicion of multisystem inflammatory syndrome in neonates:

- history of COVID-19, and
- any two of the following: cardiovascular, neurological, gastrointestinal symptoms, fever

Certainty of evidence: Low
Strength of recommendation: Strong

Recommendation 2.4.
We recommend the use of any of the following laboratory parameters to increase suspicion of multisystem inflammatory syndrome in neonates:

- CRP, interleukin-6 (IL-6), D-dimer, pro-B type natriuretic peptide (BNP), Troponin T, ferritin, lactate dehydrogenase (LDH), NT-proBNP, procalcitonin

Certainty of evidence: Low
Strength of recommendation: Strong

Guideline Panel Considerations

The GP issued a strong recommendation for the use of specific clinical and laboratory parameters to support the diagnosis of MIS-C and MIS-N, despite the low certainty of some components of the evidence base. This decision was guided by several key considerations.

First, the recommended clinical and laboratory parameters align with existing international diagnostic criteria, including those of the Centers for Disease Control and Prevention (CDC). Second, the panel discussed the prevalence of symptoms, the availability and cost of laboratory tests, and the importance of using them to support the diagnosis of multisystem inflammatory syndrome in children (MIS-C) and neonates (MIS-N).

Concerns regarding the inclusion of non-specific clinical features, such as conjunctivitis which may also occur in other conditions like Kawasaki disease were addressed by the panel. It was agreed that these signs should remain part of the diagnostic criteria, as their presence contributes to a heightened suspicion for diagnosing MIS-C.

The accessibility and affordability of recommended laboratory tests were also discussed. While CRP and ESR are widely available in most settings, other tests such as IL-6 and BNP may be costly or unavailable, or both particularly in resource-limited areas. To address this, the panel recommended that any of the suggested laboratory parameters may be used, depending on local availability, rather than mandating a specific set of tests.

To enhance diagnostic specificity, the panel set an arbitrary but pragmatic prevalence threshold of at least 50% for the inclusion of clinical and laboratory parameters in the recommendations for MIS-C and MIS-N. Since only one parameter (i.e., cardiovascular) met the threshold for neonates, the top 4 most common clinical parameters were then considered for MIS-N. As such, the panel made separate sets of recommendations for MIS-C and MIS-N.

The GP only considered history of COVID-19 as one of the criteria in the final recommendation. However, the details of established link to SARS-CoV-2 or exposure to COVID-19 as mentioned in the CDC and WHO criteria were not discussed.

Key Findings

- This evidence synthesis included two systematic reviews: Abbas *et al.* (2024), a high-quality review of 120 studies involving 20,881 MIS-C cases in children aged 0–21 years across five continents with an established link to SARS-CoV-2, and Mascarenhas *et al.* (2023), a moderate-quality review of 27 studies describing 104 neonatal MIS-N cases, primarily from Southeast Asia. Abbas *et al.* reported pooled clinical, laboratory, and demographic data using standardized MIS-C definitions, while Mascarenhas *et al.* adapted these criteria for neonates.

- In children with MIS, 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%).
- In neonates with MIS, cardiovascular symptoms (67%), neurologic signs (41%), and gastrointestinal symptoms (38%) were most frequently reported. The most elevated laboratory markers in neonates included CRP (87%), IL-6 (87%), D-dimer (81%), and BNP (79%).
- Estimates are based on systematic reviews of observational studies. The certainty of the evidence is moderate for most clinical signs and low for most laboratory markers, mainly due to variability across studies and concerns about publication bias.

Background

MIS-C is a severe post-infectious complication of COVID-19, typically occurring 3 to 4 weeks after COVID-19 infection, suggesting an immune-mediated rather than acute viral process. Since its first report in eight children in the United Kingdom[63], MIS-C has been recognized as a cause of significant morbidity and mortality, primarily affecting older children (≥5 years) and adolescents. Common comorbidities among affected individuals include obesity and asthma. While the incidence of MIS-C has gradually declined, likely due to the emergence of less virulent SARS-CoV-2 strains and increasing population immunity, its potential for severe complications continues to warrant vigilance.

Variations in the reported incidence of MIS-C in different settings across the country highlights the need for an accurate diagnosis. However, diagnosis is challenging as there are variable case definitions for MIS-C and because some clinical features of MIS-C may also be seen in other types of infections and childhood rheumatic diseases. The case definitions from the WHO,[64] United States Centers for Disease Control and Prevention (CDC),[65] and the Royal College of Pediatrics and Child Health (RCPCH)[66] have been the most commonly used (see Table 10). MIS-C cases may be misclassified depending on which case definition is used (e.g., RCPCH may include more cases as it does not require proven or probable SARS-CoV-2 infection while CDC may miss cases because of the requirement for ≥2 organ system involvement[67]).

Table 10. Current criteria used to diagnose MIS-C.

Criteria	United States CDC	WHO
Age	<21 years	0–19 years
Fever	Temperature ≥38°C for ≥24 h OR Subjective fever ≥24 h	Fever for ≥3 days
Clinical symptoms	Both of the following: 1. Severe illness (hospitalized); *and* 2. ≥2 organ systems involved	At least 2 of the following: 1. Rash, conjunctivitis, and mucocutaneous inflammation 2. Hypotension or shock 3. Cardiac involvement‡ 4. Coagulopathy 5. Acute gastrointestinal symptoms
Inflammation	Laboratory evidence of inflammation, including but not limited to, 1 or more of the following: 1. ↑ ESR 2. ↑ CRP 3. ↑ procalcitonin 4. ↑ fibrinogen 5. ↑ D-dimer 6. ↑ ferritin 7. ↑ LDH 8. ↑ IL-6 9. Neutrophilia 10. Lymphopenia 11. Hypoalbuminemia	Elevated inflammation markers, including any of the following: 1. ↑ ESR 2. ↑ CRP 3. ↑ procalcitonin

Criteria	United States CDC	WHO
Link to SARS-CoV-2	Current or recent findings of the following 1. (+) polymerase chain reaction (PCR) 2. (+) serology 3. (+) antigen test 4. COVID exposure within 4 weeks	Current or recent findings of the ff: 1. (+) PCR 2. (+) serology 3. (+) antigen test 4. likely COVID-19 contact
Exclusion	No alternative diagnosis	No obvious microbial cause

‡In the WHO case definition, cardiac involvement is defined as the presence of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including findings on echocardiogram or elevated levels of troponin / NT-proBNP.

Summary of the Evidence

Characteristics of included studies

Two systematic reviews focusing on children (Abbas 2024)[67] and neonates (Mascarenhas 2023)[68] were included in this evidence synthesis. The systematic reviews by Abbas 2024 and Mascarenhas 2023 were appraised to have "high" and "moderate" methodological quality, respectively.

Abbas *et al*. 2024 evaluated 120 records, totaling 20,881 MIS-C cases across 5 continents.[67] The population in this review included children between 0–21 years old with an established link to SARS-CoV-2 and diagnosed with MIS-C using WHO, CDC, and other standardized case definitions. The overall mean age of patients with MIS-C was 7.8 years (95% CI 7.4–8.3 years, 92 studies), with 59.5% being males. Most of the included primary studies in this review were of moderate quality (no serious risk of bias). Pooled estimates of clinical manifestations, abnormal laboratory findings, imaging studies, management strategies, demographic factors (age, gender, race), and comorbidities (obesity, asthma, systemic disease) were calculated.

Mascarenhas *et al*. 2023 focused on 27 studies (17 case reports, 7 case series, 3 cross-sectional observational studies) reporting on the characteristics and diagnostic classification of multisystem inflammatory syndrome in 104 neonates (MIS-N).[68] A large proportion (91.3%) of reported cases belonged to the Southeast Asian region, were males (60.2%), with a mean gestational age of 35.9 ± 3.3 weeks and mean birth weight of 2,255.7 ± 783.7 g. The MIS-C diagnostic criteria from WHO and CDC were modified for neonates, specifically:

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); and
5. no alternative diagnosis given to explain clinical features.

Subgroup: Children

Prevalence of specific clinical signs and symptoms in children

Almost all (99%) of children with MIS-C had **fever.** In terms of organ system involvement, **gastrointestinal** involvement was most common (70 per 100), followed by **dermatological** (60 per 100), and **cardiovascular** (64 per 100). Respiratory, musculoskeletal, renal, and neurological symptoms occurred in less than 50% of cases.

Prevalence of elevated laboratory markers in children

Most MIS-C patients had **elevated CRP** (86 per 100), **D-dimer** (81 per 100), **ESR** (66 per 100), **ferritin** (62 per 100), and **NT-proBNP** (57 per 100). High BNP, IL-6, and LDH were less common in children compared to neonates. The average values of each of these markers are listed in Table 11.

Table 11. Mean values of laboratory parameters in MIS-C and MIS-N.

Laboratory parameters	MIS-C		MIS-N	
	№ of participants	Mean laboratory values (95% CI)	№ of participants	Mean laboratory values (95% CI)
ESR (mm/hr)	1,614	53.2 (48.8–57.5)	22	14.7 (10.9–18.6)
CRP (mg/dL)	4,033	16.2 (14.9–17.6)	102	19.1 (16.6–49.0)
Ferritin (ng/mL)	3,751	567.2 (515.6–618.8)	70	407 (300.8–1,012.5)
Procalcitonin (ng/mL)	1,932	11.1 (6.5–15.8)	72	15.0 (4.0–15.0)
IL-6 (pg/mL)	1,044	151.5 (99.1–203.8)	15	42.0 (20.4–68.4)
LDH (U/L)	1,691	414.1 (348.8–479.4)	89	998.4 (983–2,362.5)
BNP (pg/mL)	1,184	1,050.4 (421.6–1,679.2)	--	--
NT-proBNP (pg/mL)	2,580	6,717.5 (5,123.5–8,311.5)	48	17,423 (7,361–30,000)
Troponin-T (ng/mL)	621	0.1 (0.0–0.2)	30	0.20 (0.11–0.92)
D dimer (ng/mL)	3,596	3,516.9 (2,970.9–4,062.9)	95	4,740.4 (1,284.5–6,570.8)

NOTE: Estimates are of LOW certainty for children due to publication bias and significant heterogeneity except for LDH (moderate certainty due to the absence of publication bias). Estimates for neonates are of LOW certainty due to very serious risk of bias due to the nature of the included study designs (case series, case reports).

Subgroup: Neonates

Prevalence of specific clinical signs and symptoms in neonates

In contrast to children, a lower proportion of neonates with MIS-N exhibited **fever** (**20 per 100)** and **dermatological signs** (**12 per 100**). The most common clinical presentation of MIS-N was **cardiac**, which occurred in **67 per 100** neonates (moderate certainty). Presentations included shock, arrhythmia with echocardiographic abnormalities, and persistent pulmonary hypertension of the newborn (PPHN). **Neurologic involvement** (e.g., encephalopathy, seizure) followed at **41 per 100**, then **gastrointestinal involvement** (e.g., abdominal distension, diarrhea, vomiting, refusal to feed) at **38 per 100.**

Prevalence of elevated laboratory markers in neonates

Most MIS-N patients had elevated laboratory markers except for ESR (5 per 100). The most common included **CRP** (87 per 100), **IL-6** (87 per 100), **D-dimer** (81 per 100), **BNP** (79 per 100), **Troponin T** (69 per 100), **ferritin** (67 per 100), and **LDH** (62 per 100). The average values of each of these markers are listed in Table 10.

GRADE summary of findings table

Tables 12 and 13 show the prevalence of clinical signs/symptoms and elevated laboratory markers in MIS-C, respectively.

Table 12. Prevalence of specific clinical signs in MIS-C and MIS-N.

Clinical signs/symptoms	№ of participants	Overall prevalence (95% CI)	Prevalence in children (95% CI)	Prevalence in neonates (95% CI)	Certainty
Fever	14,517	81% (8–100)	99% (98–99)	20% (13–29)	⊕⊕◯◯ Low
Cardiovascular[a]	18,518	64% (63–56)	64% (63–65)	67% (57–76)	⊕⊕⊕◯ Moderate
Gastrointestinal[b]	19,476	55% (33–75)	70% (69–70)	38% (29–49)	⊕⊕◯◯ Low
Conjunctivitis	12,917	55% (54–56)	55% (54–56)	Not reported	⊕⊕⊕◯ Moderate
Dermatological[c]	18,854	31% (8–71)	60% (59–61)	12% (6–19)	⊕⊕⊕◯ Moderate
Neurological[d]	18,695	27% (13–46)	17% (16–17)	41% (32–51)	⊕⊕⊕◯ Moderate
Respiratory[e]	18,823	24% (9–52)	42% (42–43)	12% (6–19)	⊕⊕◯◯ Low
Musculoskeletal[f]	12,322	19% (18–19)	19% (18–19)	--	⊕⊕◯◯ Low
Lymphadenopathy	9,165	16% (16–17)	16% (16–17)	--	⊕⊕◯◯ Low
Renal[g]	15,880	9% (2–31)	20% (20–21)	3% (1–8)	⊕⊕⊕◯ Moderate

a **Cardiovascular:** acute cardiac dysfunction, hypotension, bradycardia, tachycardia, chest pain
b **Gastrointestinal symptoms:** abdominal pain, diarrhea, nausea/vomiting, refusal to eat/loss of appetite, hepatosplenomegaly/ splenomegaly
c **Dermatological symptoms:** rash, desquamative skin, mucus membrane/oral changes
d **Neurological symptoms:** headache, seizures, altered mentation, irritability, meningismus/nuchal rigidity
e **Respiratory symptoms:** upper respiratory signs, sore throat, cough, hypoxia, rhinitis, tachypnea, distress
f **Musculoskeletal symptoms:** arthralgia, arthritis, myalgia
g **Renal symptoms:** dysuria, oliguria, hematuria

Table 13. Proportion of patients with elevated laboratory markers in MIS-C and MIS-N.

Laboratory parameters	№ of participants	Overall prevalence (95% CI)	Prevalence in children (95% CI)	Prevalence in neonates (95% CI)	Certainty
↑ CRP	7,904	86% (85–87)	86% (85–87)	87% (60–98)	⊕⊕◯◯ Low
↑ D–dimer	8,457	81% (80–82)	81% (80–82)	81% (72–88)	⊕⊕◯◯ Low
↑ Ferritin	7,652	62% (60–63)	62% (60–63)	67% (55–78)	⊕⊕◯◯ Low
↑ NT-proBNP	4,397	55% (53–57)	57% (52–59)	54% (52–56)	⊕⊕◯◯ Low
↑ IL-6	6,252	53% (9–93)	19% (18–20)	87% (60–98)	⊕⊕◯◯ Low
↑ BNP	1,971	53% (18–85)	27% (25–29)	79% (65–90)	⊕⊕◯◯ Low
↑ Troponin T	3,996	50% (49–52)	50% (49–52)	69% (39–91)	⊕⊕◯◯ Low
↑ LDH	1,624	49% (34–65)	39% (37–41)	62% (51–72)	⊕⊕⊕◯ Moderate
↑ Procalcitonin	2,228	49% (47–51)	49% (47–51)	50% (38–62)	⊕⊕◯◯ Low
↑ ESR	2,388	25% (2–84)	66% (62–67)	5% (0–23)	⊕⊕◯◯ Low

Certainty of the Evidence

The prevalence estimates were based on **low to moderate** certainty of evidence. Evidence was downgraded due to serious inconsistency across the studies included in the systematic reviews and was downgraded further in some situations if results showed high risk of publication bias. Regarding the certainty for the estimated average values for each laboratory parameter, these were based on **low** certainty of evidence due to publication bias and inconsistency (for children) or very serious risk of bias due to the inclusion of case reports and case series (for neonates), which could have overrepresented extreme cases.

Other Considerations

Resource implications (Cost/cost-effectiveness)

No research evidence identified. The cost of laboratory tests may vary per institution or area.

Stakeholder values, preferences, and acceptability

No research evidence identified.

Equity and feasibility

No research evidence identified.

Guideline Question 3.
2024–2025 COVID-19 Vaccines

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

Recommendation 3.
We suggest the use of 2024–2025 versions of monovalent COVID-19 vaccine for adults, adolescents, children, and immunocompromised individuals.

Certainty of evidence:	Very Low
Strength of recommendation:	Weak

Guideline Panel Considerations

The GP noted that the available evidence was for the 2023–2024 versions of COVID-19 vaccines. Despite the very low certainty of the available evidence, the panel recognized the public health value of updated COVID-19 vaccination. The panel emphasized that the benefits of vaccination, particularly for high-risk groups, outweigh the potential risks.

The panel highlighted several implementation and feasibility concerns. These included the high retail cost of ₱3,220.00 to ₱7,658.00 per dose, increased delivery costs in rural areas, and persistent cold chain logistics challenges, particularly for mRNA vaccines. These factors may limit equitable access since these could make the vaccine unaffordable without government subsidy and challenging to implement equitably in geographically isolated and disadvantaged communities.

The low uptake of booster doses and concerns regarding the timeliness of vaccine rollout, particularly with the rapid development of newer vaccine formulations, further complicate implementation. Vaccine hesitancy, fueled by misinformation and past controversies such as the Dengvaxia issue, remains a significant barrier to widespread acceptance, particularly in rural or less-informed populations, despite public recognition of the importance of protection against severe disease.

The panel highlighted the need for predictive modeling studies to address ongoing uncertainties regarding the evolution of COVID-19 variants and the durability of protection provided by updated vaccines.

The latest WHO recommendation on vaccine composition[69] as well as the latest statement on prevalence of variants under monitoring (VUMs)[70], released May 15, 2025 and June 25, 2025, respectively, were not discussed.

In light of these considerations, the panel supported a weak, evidence-informed recommendation for the use of updated COVID-19 vaccines, with recognition of the current limitations in direct evidence and the importance of addressing feasibility, accessibility, and public acceptance in the local context.

Key Findings

- Since there was no direct evidence available for 2024–2025 monovalent COVID-19 vaccines, the United States CDC Advisory Committee on Immunization Practices (ACIP) guidelines was adapted based on the AGREE II tool. The evidence base for CDC ACIP consisted of observational studies regarding 2023–2024 COVID-19 vaccines with no serious concerns about risk of bias, inconsistency, or imprecision.

- For adolescents and adults (age ≥12 years old), updated COVID-19 vaccines reduce the risk of medically-attended COVID-19 by 43%, hospitalization by 44% and mortality by 23% compared to those who are unvaccinated. Similarly, among infants and children (6 months to 11 years old), updated COVID-19 vaccines reduce the risk of medically-attended COVID-19 by 80%, hospitalization by 44% and mortality by 23% compared to those who are unvaccinated.
- For adults aged 65 years and older, protection from the updated COVID-19 vaccine against medically-attended illness and hospitalization declined substantially over time, showing little to no benefit by 4 to 10 months after vaccination. However, the vaccine may still offer moderate protection against severe outcomes such as thromboembolic events, intensive care unit admission, and death within the first 5 months, but the evidence is very uncertain.
- Among moderately or severely immunocompromised adults, vaccine effectiveness against hospitalization also declined over time, from modest protection shortly after vaccination to very little or no benefit by 4 to 6 months, but the evidence is very uncertain.
- The incidence of pre-specified serious adverse events which include anaphylaxis, and myocarditis/pericarditis were rare.
- The overall certainty of evidence was very low because it was downgraded for indirectness since pooled evidence was based on the 2023–2024 monovalent COVID-19 vaccine. Moreover, data for infants and children were mostly indirect outcomes derived from adolescents and adults.

Background

With the lifting of the state of public health emergency due to COVID-19 in July 2023,[71] COVID-19 testing rates in the Philippines declined sharply. Reported daily cases in December of 2023 averaged 500 (3.135 per million people), while testing dropped from 78,280 tests during the same period last year to just 2,234 as hospitals and institutions eased routine testing requirements.[72,73] Consequently, the actual incidence of COVID-19 in the Philippines remains unknown. Although hospitalization and death rates have remained relatively low in the general vaccinated population, elderly and immunocompromised individuals continue to be vulnerable, based on indirect data from the United Kingdom and the United States.[74,75] This vulnerability is partly attributed to shifts in circulating strains and the potential for immune evasion among those immunized with non-specific COVID-19 vaccines. The antigenically distinct KP.2 and JN.1 strains of the Omicron variant now predominate worldwide.[76] However, local sequencing efforts have analyzed only 287 samples, with no new cases detected in the past four weeks. The JN.1 strain was first identified in September 2023,[77] while KP.2, a descendant of JN.1, was designated a variant under monitoring in May 2024.[78] These developments led to the formulation of monovalent vaccines targeting the spike proteins of JN.1 and KP.2 for the 2024–2025 vaccination cycle.

Several monovalent COVID-19 vaccines have received emergency use authorization from the Philippine Food and Drug Administration (FDA). However, many vaccines recommended in the 2023 Philippine Clinical Practice Guidelines (e.g., Vaxzevria, CoronaVac, Jcovden) lack specificity against Omicron variants. Among the authorized monovalent vaccines, only two mRNA vaccines (Spikevax and Comirnaty) and one protein subunit vaccine (Nuvaxovid/Covovax) were relevant to the research question. The primary aim of this review is therefore to determine whether these 2024–2025 versions of the COVID-19 vaccine should be given to adults, adolescents, and children in the Philippines to prevent COVID-19.

Summary of the Evidence

Characteristics of included studies

Primary studies using the 2024–2025 vaccines were sought, however none met the inclusion criteria except for one ongoing study expected to conclude by April 2025.[79] With no direct evidence available, the next best evidence came from the 2023–2024 COVID-19 vaccines, which formed the basis of the nine guidelines and guidance documents.[80-87] Following the DOH Manual for Clinical Practice Guideline Development and the GRADE-ADOLOPMENT Process,[88]

the AGREE II tool was used to appraise these guidelines. The highest rating (96% overall, 88% for rigor of development) came from the United States CDC ACIP guidelines.[80]

The United States CDC guidelines were selected for adopting similar *a priori* outcomes: COVID-19 incidence, severe disease, hospitalization, mortality, and safety. Specifically, efficacy outcomes included medically attended COVID-19 cases (i.e., emergency department or urgent care visits), COVID-19 hospitalizations, and COVID-19-related deaths for adolescents, adults, infants, and children. Safety outcomes covered specific adverse events: anaphylaxis and myocarditis or pericarditis for adults and adolescents (aged ≥12 years old), with MIS-C added for infants and children (6 months to 11 years of age).

Efficacy outcomes: Adolescents and adults (≥12 years old)

Medically-attended COVID-19

All efficacy outcomes were expressed in terms of **vaccine effectiveness (VE)**. VE refers to the ability of the vaccine to prevent specific outcomes in a real-life situation. It is proportional to vaccine potency or efficacy but is affected by several factors including the target population, storage, administration, cost and accessibility. It is expressed as a rate difference and uses the odds ratio (OR) of developing the outcome despite vaccination.

The updated COVID-19 vaccine may reduce the risk of medically-attended COVID-19 (i.e., emergency department and urgent care visits) in adolescents and adults aged ≥12 years (pooled VE: 43%, 95% CI 30–54%), but the evidence is very uncertain due to very low certainty of evidence (5 observational studies, N = 27,478 cases / 190,528 controls).

Hospitalization

The updated COVID-19 vaccine may reduce the risk of hospitalization due to COVID-19, with a pooled VE of 44% (95% CI 34–52%), but the evidence is very uncertain due to very low certainty (8 observational studies, N = 24,878 cases / 166,023 controls).

Death

The updated COVID-19 vaccine may reduce the risk of death from COVID-19, with a pooled VE of 38% (95% CI 8–36%), but the evidence is very uncertain due to very low certainty of evidence (3 observational studies, N = 1,130 / 343,558 exposed vs. 955 / 50,504,700 unexposed).

Efficacy outcomes: Infants and children (6 months to 11 years old)

Medically-attended COVID-19

Among infants and children, one study demonstrated that the updated COVID-19 vaccine reduced medically-attended COVID-19 (i.e., emergency department and urgent care visits) (VE: 80%, 95% CI 42–96%)

Hospitalization and death

The updated COVID-19 vaccine exhibited an effectiveness of 44% (95% CI 34–52%) in reducing hospitalization risk and 38% (95% CI 8–36%) for death. Effects of vaccination on children were based on estimates from adolescents and adults but further downgraded due to very serious indirectness.

Efficacy outcomes: Older adults (≥65 years old)

Medically-attended COVID-19

Analysis of data (September 2023 to August 2024) from Virtual SARS-CoV-2, Influenza, and Other respiratory viruses Network (VISION) showed that for adults ≥65 years old, VE for medically-attended COVID-19 decreased to 20% (95% CI 11–27%) at 120-179 days after vaccination which further decreased to VE 1% (95% CI -7–8%) at 180-299 days after vaccination.

Hospitalization

For the same age group, VE for hospitalization decreased to 19% (95% CI 7–30%) at 120–179 days after vaccination. There was further decrease to VE -4% (95% CI -16–7%) at 180–299 days after vaccination.

Thromboembolic events, deaths, and intensive care unit (ICU) admission or death

VE against critical outcomes was as follows: (i) thromboembolic events (median follow-up of 74 days) remained at 53% (95% CI 23–71%); (ii) death (median follow-up of 104 days) at 47% (95% CI 15–67%); and (iii) ICU admission/death at 43% (95% CI 18–60%) at <5 months after vaccination.[89]

Efficacy outcomes: Moderately or severely immunocompromised adults (≥18 years old)

Hospitalization

Analysis of data from VISION (September 2023–August 2024) showed that for immunocompromised adults ≥18 years old, VE for hospitalization was at 36% (95% CI 22–48) less than 2 months after vaccination. It decreased to VE 23% (95% CI 6–36%) at 60–119 days after vaccination which further decreased to VE 1% (95% CI -28–23%) at 120–179 days after vaccination.[89]

Safety outcomes

Myocarditis and Pericarditis *(2 observational studies, very low certainty)*

Observational data on serious adverse events were reviewed. One analysis from Vaccine Safety Datalink (VSD) evaluated chart-reviewed cases of myocarditis and pericarditis occurring in a 0–7-day risk interval among persons aged 5 to 39 years following a booster dose of the original monovalent vaccine and a booster dose of the bivalent vaccine.

The rate of myocarditis and pericarditis per million doses varied by age group, sex, vaccine, and dose. For children ages 5 to 11 years, there were no cases of myocarditis or pericarditis observed. For adolescents and adults, the highest incidence rate of myocarditis and pericarditis was observed among males ages 16 to 17 years receiving the original monovalent Pfizer booster dose (188.0, 95% CI 86.0–356.9 per million doses). The highest incidence rate following a bivalent booster dose was observed among males 30–39 years receiving the Moderna vaccine (23.9, 95% CI 0.6–133.2 per million doses), however due to low uptake of the bivalent booster, incidence rates of myocarditis and pericarditis should be interpreted with caution.

Anaphylaxis *(1 observational study, very low certainty of evidence)*

One analysis of data from VSD evaluated chart-reviewed cases of anaphylaxis among all vaccinated persons aged ≥12 years following either dose of the original monovalent primary series was conducted. Based on events occurring in a 0–1-day risk interval after vaccination, the estimated incidence rates of confirmed anaphylaxis were 5.1 (95% CI 3.3–7.4) per million doses of Moderna, and 4.8 (95% CI 3.2–6.9) per million doses of Pfizer. Due to low uptake, there were no data to inform harms of Novavax in VSD.

GRADE summary of findings table

Tables 14–17 show the outcomes of 2023–2024 COVID-19 vaccines in adolescents and adults (≥12 years old), infants and children (6 months to 12 years old), the elderly (≥65 years old), and the immunocompromised, respectively.

Table 14. Summary of outcomes of 2023–2024 COVID-19 vaccines in adolescents and adults (≥12 years old).

Critical outcomes	Basis (№ and type of studies, total participants)	Effect estimate	95% CI	Interpretation	Certainty of evidence
Medically attended COVID-19 (emergency department / urgent care visits)	5 observational studies (N = 27,478 cases, 190,528 controls)	VE 43	30, 54	Benefit	⨁◯◯◯ Very low[a,b]
Hospitalization	8 observational studies (N = 24,878 cases, 166,023 controls)	VE 44	34, 52	Benefit	⨁◯◯◯ Very low[a,b]
Death	3 observational studies (N = 1,130 cases, 343,558 controls)	VE 23	8, 36	Benefit	⨁◯◯◯ Very low[a,b]
Serious adverse events (anaphylaxis, myocarditis/pericarditis)	2 observational studies	Highest incidence rate of myocarditis and pericarditis among males ages 16–17 years receiving the original monovalent Pfizer booster dose (188.0, 95% CI 86.0–356.9 per million doses). The highest incidence rate following a bivalent booster dose was observed among males 30–39 years receiving the Moderna vaccine (23.9, 95% CI 0.6–133.2 per million doses). Estimated incidence rates of confirmed anaphylaxis were 5.1 (95% CI 3.3–7.4) per million doses of Moderna, and 4.8 (95% CI 3.2–6.9) per million doses of Pfizer.		Inconclusive	⨁◯◯◯ Very low[a,b]

a Observational study design limitations
b Serious indirectness

Table 15. Summary of outcomes of 2023–2024 COVID-19 vaccines in infants and children (6 mo to 11 y old).

Critical outcomes	Basis (№ and type of studies, total participants)	Effect estimate	95% CI	Interpretation	Certainty of evidence
Medically attended COVID-19	1 observational study (N = 1,331 cases, 29,133 controls)	VE 80	42, 96	Benefit	⊕◯◯◯ Very low[a,b]
Hospitalization	8 observational studies (N = 24,878 cases, 166,023 controls)	VE 44	34, 52	Benefit	⊕◯◯◯ Very low[a,b]
Death	3 observational studies (N = 1,130 cases, 343,558 controls)	VE 23	8, 36	Benefit	⊕◯◯◯ Very low[a,b]
Serious adverse events (anaphylaxis, myocarditis/pericarditis)	1 observational study	For children ages 5 to 11 years, there were no cases of myocarditis or pericarditis observed.		Inconclusive	⊕◯◯◯ Very low[a,b]

a Observational study design limitations
b Serious indirectness

Table 16. Summary of outcomes of 2023–2024 COVID-19 vaccines in the elderly (≥65 years old).

Critical outcomes	Basis (№ and type of studies, total participants)	Effect estimate	95% CI	Interpretation	Certainty of evidence
Medically attended COVID-19 infection 4 to 6 months after vaccination	1 observational study	VE 20	11, 27	Benefit	⊕◯◯◯ Very low[a,b]
Medically attended COVID-19 infection ≥6 months after vaccination	1 observational study	VE 1	-7, 8	Inconclusive	⊕◯◯◯ Very low[a,b]
Hospitalization 4 to 6 months after vaccination	1 observational study	VE 19	7, 30	Benefit	⊕◯◯◯ Very low[a,b]
Hospitalization ≥6 months after vaccination	1 observational study	VE -4	-16, 7	Inconclusive	⊕◯◯◯ Very low[a,b]
Thromboembolic events (median follow-up 74 days)	1 observational study	VE 53	23, 71	Benefit	⊕◯◯◯ Very low[a,b]
Death (median follow-up 104 days)	1 observational study	VE 47	15, 67	Benefit	⊕◯◯◯ Very low[a,b]
ICU admission/ death (median follow-up 149 days)	1 observational study	VE 43	18, 60	Benefit	⊕◯◯◯ Very low[a,b]

a Observational study design limitations
b Serious indirectness

Table 17. Summary of outcomes of 2023–2024 COVID-19 vaccines in immunocompromised adults.

Critical outcomes	Basis (№ and type of studies, total participants)	Effect estimate	95% CI	Interpretation	Certainty of evidence
Hospitalization <2 months after vaccination	1 observational study	**VE 36%**	22, 48	Benefit	⊕◯◯◯ Very low[a,b]
Hospitalization 2-4 months after vaccination	1 observational study	**VE 23%**	6, 36	Benefit	⊕◯◯◯ Very low[a,b]
Hospitalization 4-6 months after vaccination	1 observational study	**VE 1%**	-28, 23	Inconclusive	⊕◯◯◯ Very low[a,b]

a Observational study design limitations
b Serious indirectness

Certainty of the Evidence

Overall, the certainty of evidence is rated as **very low**.

Evidence for adults and adolescents came from observational studies, including preprints, with no serious concerns about risk of bias, inconsistency, or imprecision.[80] Similarly, outcomes for infants and children are based on observational studies with no major concerns about bias, inconsistency, or imprecision. However, hospitalization, death, and serious adverse events due to COVID-19 were downgraded for indirectness, as the evidence was drawn from studies on adults and adolescents. Since these outcomes are based on 2023–2024 vaccines which were mostly trials conducted in the United States,[80] certainty of evidence is further downgraded for indirectness.

Evidence for subgroup analysis among individuals with risk factors was primarily derived from non-randomized, indirect studies. For the elderly subgroup, the certainty of evidence was downgraded due to risk of bias (since the data originated from internal United States CDC reports) and indirectness, as the evidence was based on earlier vaccine versions and drawn from heterogeneous population groups.

Other Considerations

Estimated costs

The retail costs (cost of good, excluding distribution and administration costs) of privately sold vaccines are approximately as follows: Spikevax US$129.00–US$141.80 (₱7,224.00–₱7,940.80) per dose in the United States;[90] Novovax US$141.70 (₱7,935.20) per dose in the United States;[90] and Pfizer US$57.50–US$136.75 (₱3,220.00–₱7,658.00) per dose in the United States,[90] £79–£99 (₱5,925–₱7,425) in the United Kingdom.[91] These prices are not the negotiated rates between governments and manufacturers and are therefore likely overestimated. Local data from 2022 estimated routine COVID-19 vaccine delivery costs at ₱179–₱656 per dose, reflecting lower delivery volumes. This estimate, based on a payer perspective, included costs across all levels of the health system, including contributions from development partners and donors. The report also highlighted that lower vaccine delivery volumes are associated with higher per-dose costs. This is particularly relevant given the wide variation across regions, with delivery costs notably lower in urban areas compared to rural ones. Moreover, for the current 2024–2025 vaccine, costs are expected to be higher in the absence of routine vaccination programs.[92]

Cost-effectiveness of vaccination

Vaccination and vaccination campaigns were both deemed cost-effective based on two studies. The first study, a cost-effectiveness study from the United States, assessed the 2024–2025 COVID-19 vaccine compared to no vaccination using a payer perspective. For individuals over 65 years of age, the ICER was dominant (i.e.,cost-

saving). For those over 18 years of age, the ICER was US$18,289 (₱1,024,184) per QALY, below their US$50,000 (₱2,800,000) willingness-to-pay (WTP) threshold.[74] In the United Kingdom, a similar study from a healthcare perspective compared the 2024 Moderna vaccination campaign to no vaccination campaign. The estimated ICER was £8,540 (₱640,500) per QALY gained when the campaign was targeted to adults ≥65 years of age, which is well below their £20,000 (₱1,500,000) WTP threshold.[75] No similar cost-effectiveness studies, even for prior COVID-19 vaccines, have been found for the Philippines.

Stakeholder values, preferences, and acceptability

The COVID-19 National Vaccination Program (CNVP) initially aimed to vaccinate 70 million individuals (63% of the eligible population) in 2021. The target was increased to 70% of the eligible population (approximately 77 million individuals) for 2022. While the Philippines achieved a 45.37% vaccination rate in 2021, which increased to 66.12% in 2022, booster dose uptake remained low. Vaccine hesitancy, fueled by fear, misinformation, and concerns about adverse effects, contributed to this low uptake.[93]

Results suggest that young participants and those with higher education levels are more likely to take the vaccine as the proportion of unvaccinated individuals increases with age. Those who indicated that the COVID-19 vaccines are safe and needed to protect one's health were more likely to get vaccinated. Participants who know about vaccine brands, compositions, and doses, as well as vaccination effectiveness and side effects after vaccination being considered normal, have a higher tendency to decide to get vaccinated than those with little or no knowledge of these things. Those who have public health insurance are more likely to get vaccinated.[94] Sex, employment status, and family income were unrelated to the study's vaccination decision, probably because the Philippine government made COVID-19 vaccines free for all its citizens; thus, financial incapacity and unemployment did not deter anyone from getting vaccinated. Men and women received the vaccines to comply with institutional requirements. Employees generally opted to get vaccinated.

People with long standing illness were not likely to get vaccinated against COVID-19. Vaccine hesitancy remains to be an issue among those with health problems. The lowest confidence rating was related to the vaccine's side effects, followed by doubt about its safety.[94] The decline in the COVID-19 vaccine confidence in the Philippines may have been influenced by the Dengvaxia vaccine fiasco in 2017. The controversy caused the vaccine confidence of Filipinos to decline from 93% in 2015 to 32% in 2018.[95] Traumatic experiences concerning previous vaccination and information obtained from traditional, social media, and neighbors further contribute to delay and refusal of vaccination.[96]

The likelihood of getting vaccinated decreases as the region gets further away from the NCR as urbanization significantly determines the vaccine acceptance rate. Vaccine awareness of participants in this study is generally high as most lived in urban areas. There was high awareness in NCR and Luzon.[94]

Equity and feasibility

A preprint reported that COVID-19 mortality rates per 100,000 population were highest in Benguet, followed by Cagayan and Bataan. The study identified poverty incidence and hospital bed availability per 100,000 population as independent predictors of mortality.[97] However, it did not account for vaccination as a confounder, though it included mortality data from 2020–2023 (note that the first COVID-19 vaccine in the Philippines was delivered in March 2021). While vaccination can prevent deaths, its incremental benefit is likely greater in impoverished areas. However, vaccination coverage remains uneven. NCR has the highest vaccination rates, whereas the Cordillera Administrative Region (CAR), where Benguet is located, has the lowest.[98] At an individual level, vaccine uptake in the Philippines is also influenced by age, educational attainment, and awareness of COVID-19 vaccination.[94]

Equitable distribution was influenced not only by geographic factors but also by socioeconomic status, exposure to (mis)information, social influence, and deeply rooted religious beliefs, all of which historically shaped COVID-19 vaccine perceptions and, ultimately, uptake.[99]

Evidence suggests that COVID-19 vaccination can be feasibly integrated into primary care and may even serve as a facilitator for integrating other public health interventions in primary care.[100] However, cold chain requirements remain a challenging feasibility issue. For example, the Moderna vaccine must be stored at –50°C to –15°C until its expiration date, or at 2°C to 8°C for up to 30 days.[101] Another concern is the timeliness, relevance, and availability of the 2024–2025 vaccine, given that Pfizer has already begun marketing a 2025–2026 formula ahead of FDA approval.[102]

Guideline Question 4.
Alternative Leptospirosis Prophylaxis

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

Recommendation 4.1.
We suggest the use of azithromycin as an alternative post-exposure prophylaxis for leptospirosis in adults.

Certainty of evidence:	Very Low
Strength of recommendation:	Weak

Recommendation 4.2.
We suggest the use of amoxicillin as an alternative post-exposure prophylaxis for leptospirosis in adults.

Certainty of evidence:	Very Low
Strength of recommendation:	Weak

Recommendation 4.3.
We recommend against the use of cephalosporin as an alternative post-exposure prophylaxis for leptospirosis in adults.

Certainty of evidence:	Very Low (no evidence)
Strength of recommendation:	Strong

Guideline Panel Considerations

The GP noted that the included study compared azithromycin, amoxicillin, and cephalosporin to doxycycline. Panel members also considered indirect evidence comparing azithromycin and penicillin to no intervention.

A weak recommendation for the use of azithromycin as an alternative post-exposure prophylaxis is made based on very low certainty evidence. Despite the absence of direct evidence for its use in post-exposure settings, its potential efficacy for pre-exposure prophylaxis, acceptable safety profile, and oral route of administration make it a reasonable alternative, particularly in settings where doxycycline is unavailable, contraindicated, or impractical to deploy. The recommendation reflects both the need for feasible alternatives in high-risk, flood-prone, or rural communities and the uncertainty of current evidence.

A weak recommendation for the use of amoxicillin as an alternative post-exposure prophylaxis is similarly based on very low certainty evidence. While no direct research evidence supports its use for prophylaxis, amoxicillin is known to be effective in the treatment of mild leptospirosis based on the National Antibiotic Guidelines, [103] is widely available, affordable, and generally well tolerated. Its accessibility in resource-limited settings, particularly where

doxycycline or azithromycin may not be suitable, contributed to the recommendation, while acknowledging the substantial uncertainty regarding its preventive effectiveness.

A strong recommendation against the use of cephalosporins for post-exposure prophylaxis is made, given the complete absence of evidence supporting their effectiveness in this role.

Overall, the GP recognized significant logistical challenges in the pre-positioning and rapid deployment of doxycycline, particularly in rural and flood-prone communities where the burden of leptospirosis is highest. The panel also acknowledged the absence of direct evidence for alternative antibiotics as post-exposure prophylaxis but emphasized the practical need for feasible, accessible alternatives in settings where doxycycline may not be readily available. Indirect evidence and clinical judgment guided the panel's cautious or weak recommendations, reflecting both the potential benefits and the limitations of the current evidence base.

Key Findings

- One RCT with 137 individuals compared azithromycin to doxycycline for pre-exposure prophylaxis against leptospirosis. No research evidence was identified evaluating the effectiveness and safety of azithromycin, cephalosporin, or amoxicillin as post-exposure prophylactic alternatives to doxycycline.
- The study found inconclusive evidence regarding the prevention of both laboratory-confirmed and clinically diagnosed leptospirosis when using azithromycin instead of doxycycline as prophylaxis.
- Non-serious adverse events such as epigastric pain and urticaria (azithromycin group), and heartburn, photosensitivity, and vertigo (doxycycline group), were reported without a clear benefit favoring either treatment. Serious adverse events were not among the outcomes reported.
- Serious concerns over the risk of bias (including missing details on the randomization and allocation concealment methods, and potential selective outcome reporting), indirectness, and imprecision led to a very low overall certainty of evidence.

Background

Leptospirosis is a zoonotic systemic infection caused by *Leptospira interrogans* that may cause extensive vasculitis leading to complications such as pulmonary hemorrhage, renal failure and hemolysis. It presents a significant public health challenge, particularly in regions frequently affected by flooding such as the Philippines.[104] The standard post-exposure prophylactic treatment, doxycycline, has been shown to reduce the duration of illness and alleviate symptoms such as fever and malaise in mild cases.[105,106] However, while doxycycline is effective for milder forms of the disease, some studies have reported limited benefits in reducing mortality and managing severe cases,[107,108] thereby prompting concerns about its overall efficacy. Considering these limitations and the potential for doxycycline shortages, especially in flood-prone areas increasingly impacted by climate change, there is a clear need to explore alternative therapeutic options.

This review evaluates azithromycin, cephalosporin, and amoxicillin as alternative post-exposure prophylaxis for leptospirosis. Though commonly used for treatment, their prophylactic potential remains unclear. The review explores whether these antibiotics can match the preventive benefits of doxycycline, which is crucial for maintaining effective prophylaxis when doxycycline is unavailable, especially during resource-limited outbreaks.

Summary of the Evidence

Characteristics of included study

No RCTs were found comparing doxycycline with other antibiotics for *post*-exposure prophylaxis. Four RCTs[109-112] and 1 non-randomized study of intervention[113] were initially identified during the search but were excluded because their control groups received only a placebo or no intervention. No research evidence was identified for

the effectiveness and safety of cephalosporin and amoxicillin as alternatives to doxycycline for leptospirosis prophylaxis.

Evidence for this comparison was obtained from 1 double-blind RCT[114] (Alikhani 2018) comparing azithromycin vs. doxycycline pre-exposure prophylactic regimens. Although the study enrolled 200 adults aged 18–65 years across three treatment arms (azithromycin, doxycycline, and placebo), only the data from the azithromycin (N = 66) and doxycycline (N = 71) arms were included in our analysis, resulting in a total of 137 participants. This study was conducted in a single center in Iran among residents of an endemic area who worked in paddy fields (considered a high-risk group). Both drugs were given as pre-exposure prophylaxis.

Outcome measures assessed during the 12-week prophylaxis period included clinical symptoms (fever, body pain, red eye, calf pain, icterus) and laboratory markers for leptospirosis (IgG at 0, 6, and 12 weeks; IgM at 2nd week after disease onset).

Efficacy outcomes: Azithromycin vs. doxycycline (1 RCT, N = 137, very low certainty)

Reduction of leptospirosis

It was unclear if azithromycin was better or worse than doxycycline in reducing the risk of clinically confirmed leptospirosis (regardless of laboratory confirmation). In the included trial, 8 out of 71 participants (12.7%) in the doxycycline group developed clinical leptospirosis compared to 5 out of 66 participants (7.6%) in the azithromycin group. This corresponds to a risk ratio (RR) of 0.24 (95% CI 0.05–1.07; $p = 0.06$). In absolute terms, **azithromycin was associated with 9.6% fewer leptospirosis cases (as low as 12 fewer to 0.9 more cases per 100 participants)** compared to doxycycline. However, this effect is highly imprecise and very uncertain.

Safety outcomes: Azithromycin vs. doxycycline (1 RCT, N = 137, very low certainty)

Non-serious adverse events

Non-serious adverse events were observed in both treatment groups. In the **doxycycline group, 6 out of 71 participants (8.5%) experienced adverse events,** specifically heartburn (n = 2), photosensitivity (n = 3), and vertigo (n = 1). On the other hand, **the azithromycin group, 5 out of 66 participants (7.6%) reported non-serious adverse events**, including epigastric pain (n = 4) and urticaria (n = 1). The corresponding RR comparing azithromycin to doxycycline was 0.90 (95% CI 0.29–2.80; $p = 0.85$).

Serious adverse events

Serious adverse events were not reported as an outcome of interest in the sole RCT[114] included in this review.

Efficacy and safety outcomes: Cephalosporin vs. doxycycline

No research evidence was identified for the effectiveness and safety of cephalosporin as an alternative to doxycycline for leptospirosis prophylaxis.

Efficacy and safety outcomes: Amoxicillin/penicillin vs. doxycycline

No research evidence was identified for the effectiveness and safety of amoxicillin/penicillin as an alternative to doxycycline for leptospirosis prophylaxis.

GRADE summary of findings table

Table 18 shows the efficacy and safety outcomes in azithromycin vs. doxycycline for leptospirosis.

Table 18. Azithromycin compared to doxycycline for leptospirosis.

Outcomes	Basis (№ and type of studies, total participants)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty of Evidence
			Doxycycline	Azithromycin	Difference	
Efficacy outcomes						
Clinical diagnosis of leptospirosis regardless of laboratory confirmation	1 RCT (N = 137)	**RR 0.24** (0.05–1.07)	12.7%	3.0% (0.6–13.6)	**96 fewer cases per 1,000** (120 fewer to 9 more)	⊕◯◯◯ Very low[a,b,c]
Safety outcomes						
Serious adverse events	1 RCT (N = 137)	Not reported	N/A	N/A	N/A	N/A
Non-serious adverse events	1 RCT (N = 137)	**RR 0.90** (0.29–2.80)	8.5%	7.6% (2.5–23.7)	**8 fewer cases per 1,000** (60 fewer to 152 more)	⊕◯◯◯ Very low[a,c]

a Downgraded one level for risk of bias (no information on randomization, allocation concealment, and selection of reported result).
b Downgraded one level for indirectness since the study evaluates pre-exposure prophylaxis, whereas the guideline focuses on post-exposure prophylaxis
c Downgraded three levels for imprecision (the optimal information size criterion was not met, i.e. sample size fewer than the optimal information size of 16,528 participants, very wide CIs in the result, and 95% CI included both benefits and harms).

Certainty of the Evidence

The overall certainty of evidence was downgraded to **very low** due to serious concerns about risk of bias (including issues in randomization and possible selective outcome reporting), indirectness (as the study assessed pre-exposure rather than post-exposure prophylaxis), and imprecision (due to wide confidence intervals and a small number of events, leading to uncertainty in the effect estimate).

Other Considerations

Costs

For specific local costs of antibiotics, Table 19 presents the estimated ranges based on the 2024 DPRI of the DOH.[115] Based on this data, the estimated costs of azithromycin, amoxicillin, and cephalosporins are generally higher than that of doxycycline. No local cost-effectiveness studies on doxycycline for leptospirosis prophylaxis have been conducted.

Table 19. Antibiotics and their local unit cost estimates based on the 2024 DPRI[115] Price Range (₱).

Drug Name	Formulation	DPRI Unit Price (₱)		Average Prophylaxis Course Cost
		Lowest	Highest	
Control				
Doxycycline	100 mg capsule	1.21	12.00	13.21
Intervention				
Azithromycin	200 mg/5 mL (15 mL) 200 mg/5 mL (60 mL) 500 mg tablet	55.00 118.00 3.60	386.60 138.00 101.64	220.80 128.00 54.42
Amoxicillin	100 mg/mL (15 mL) 250 mg/5 mL (60 mL) 250 mg capsule 500 mg capsule	18.80 3.80 1.93 1.19	57.75 90.00 4.88 6.00	*Cannot estimate** *Cannot estimate** *Cannot estimate** *Cannot estimate**
Cephalosporins Ceftriaxone Cefotaxime	 1 g vial 500 mg vial	 16.43 98.89	 538.50 927.98	 *Cannot estimate** *Cannot estimate**

Note: *Course cost estimates are based on typical adult prophylactic dosing, where applicable.*
**Some formulations are excluded from course costing due to treatment-only indications.*

Cost-effectiveness

There is currently no local health economic evidence comparing the cost-effectiveness of azithromycin or any other antibiotics with doxycycline for prophylaxis against leptospirosis. Although a cost-effectiveness study using both United States and Barbados pricing[116] demonstrated that prophylactic antibiotic use is more cost-effective than no prophylaxis, it did not directly compare doxycycline with other agents.

Stakeholder values, preferences, and acceptability

In this context, understanding community readiness and acceptance of alternative regimens becomes crucial. Based on a local study conducted in Laguna, stakeholder acceptability for prophylactic alternatives to doxycycline may be supported by the community's generally positive attitudes towards leptospirosis prevention.[117] Despite limited knowledge and suboptimal practices, especially among agricultural workers, respondents exhibited high willingness to adopt protective measures when properly informed. The study showed that higher knowledge and positive attitudes were significantly associated with improved prevention practices. Moreover, broadcast media were identified as a strong channel for influencing behavior, suggesting that clear and accessible messaging around alternative prophylaxis (e.g. azithromycin) could be well-received. These findings indicate that, with appropriate health education and communication strategies, communities, particularly those at high risk, are likely to accept alternative prophylactic regimens when doxycycline is unavailable.[117] This supports the feasibility of integrating such alternatives into public health programs.

Similarly, a study conducted among pedicab drivers in flood-prone urban areas of Manila highlighted major gaps in leptospirosis-related knowledge and preventive practices.[118] Only 21% demonstrated satisfactory preventive behavior, and those with poor knowledge, particularly individuals with low education levels, were significantly more likely to engage in unsafe practices. This suggests that equity concerns must be addressed when introducing prophylactic alternatives, especially for marginalized groups. Tailored health communication and community-based interventions, particularly in low-income urban settings, can enhance the acceptability and feasibility of alternative prophylaxis strategies.

Equity and feasibility

Doxycycline remains the recommended drug for leptospirosis prophylaxis, however recent reports have highlighted concerns over its supply, particularly during surges in cases following flooding events. In July 2023, the DOH reassured the public of ongoing coordination with the Department of Budget and Management to secure additional stocks amid rising leptospirosis cases in NCR and other flood-affected areas. However, the same report also acknowledged logistical challenges in pre-positioning and rapid deployment of doxycycline to highly affected regions.[119] Additionally, the Philippine government has pushed for expedited regulatory clearance of doxycycline to ensure timely availability during outbreaks, emphasizing the importance of stockpiling and proactive procurement.[120] These situations underscore the need to explore and validate alternative prophylactic options that could serve as substitutes during supply disruptions.

Guideline Question 5.
Leptospirosis Prophylaxis for Children and Pregnant Women

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

Recommendation 5.1.
We suggest the use of azithromycin for children <8 years of age and pregnant women as post-exposure prophylaxis for leptospirosis.

Certainty of evidence: Very Low
Strength of recommendation: Weak

Recommendation 5.2.
We suggest the use of amoxicillin for children <8 years of age and pregnant women as post-exposure prophylaxis for leptospirosis.

Certainty of evidence: Very Low
Strength of recommendation: Weak

Recommendation 5.3.
We recommend against the use of cephalosporin for children <8 years of age and pregnant women as post-exposure prophylaxis for leptospirosis.

Certainty of evidence: Very Low (no evidence)
Strength of recommendation: Strong

Guideline Panel Considerations

The GP recognized the significant burden of leptospirosis in the Philippines, particularly among vulnerable groups such as children under 8 years old and pregnant women, who are excluded from standard doxycycline prophylaxis due to safety concerns. This limitation creates an urgent need for potential alternative prophylactic options that can be deployed in high-risk settings, such as during flood-related outbreaks.

Although short-course doxycycline prophylaxis is standard in adults, it is contraindicated in young children and pregnant women due to potential adverse effects, such as teeth discoloration. Nonetheless, the panel mentioned that the Pediatric Infectious Disease Society of the Philippines (PIDSP) Clinical Practice Guidelines (CPG) from 2019 acknowledged the potential use of short-course doxycycline for leptospirosis prophylaxis in children, noting that clinically significant teeth discoloration has not been observed with short-term use.

Despite the very low certainty of evidence, the panel suggests the conditional use of azithromycin and amoxicillin as alternative post-exposure prophylactic options in these populations. The weak recommendation reflects the extremely limited and indirect nature of the available evidence.

The panel recommends against the use of cephalosporins for post-exposure prophylaxis in these populations, due to the complete absence of supporting research evidence.

The recommendations also consider practical factors, including the high disease burden in flood-prone regions, the logistical challenges of delivering prophylaxis during public health emergencies, and the need to balance potential benefits with safety concerns, particularly in children and pregnant women. There is a critical need for high-quality research, evaluating the efficacy and safety of azithromycin, amoxicillin, and other potential alternatives in these population groups.

Key Findings

- Two retrospective observational studies reported on the incidence of leptospirosis cases following chemoprophylaxis programs during flooding incidents. One study used azithromycin, while the other study used amoxicillin for children and pregnant women. Both studies reported the incidence of leptospirosis following the flooding, but neither stratified the outcome based on receipt of chemoprophylaxis nor the target population (children or pregnant), nor was a control group identified. Adverse events were not reported in both studies.
- The study in Mumbai identified 59 (38 per 100,000) PCR-confirmed leptospirosis, while the study in Guyana reported 236 (78 in 100,000) suspected leptospirosis cases in the locality after the flooding incidents. However, the reported cases included all populations who received chemoprophylaxis, with no data specific to pregnant women and children <8 years old.
- Both studies had high risk of bias and serious concerns for indirectness, which contributed to the downgrading of the evidence to very low certainty for the outcome of leptospirosis incidence. No research evidence was identified for the safety of azithromycin and amoxicillin, and for the safety and efficacy of cephalosporins as post-exposure prophylaxis for leptospirosis among children <8 years old and pregnant women.

Background

In 2023, locally reported cases to the DOH revealed 158 cases of leptospirosis among children 9 years old and below, and 46 cases among the reproductive age group (15 to 49 years old).[121] While doxycycline remains the standard post-exposure prophylaxis among individuals exposed to flood water, it is contraindicated among children less than 8 years old and pregnant women due to risk of teeth discoloration in the fetus, infancy, and childhood.[122] Hence there is a need to evaluate alternative prophylactic antibiotics for leptospirosis for this target population.

Alternative drugs active against *Leptospira* that are used for the treatment of leptospirosis as stated in the DOH National Antibiotic Guidelines include azithromycin, penicillin, ampicillin, amoxicillin, cefotaxime, and ceftriaxone.[103] This review evaluates the role of azithromycin, cephalosporins, and amoxicillin as post-exposure prophylaxis among children less than 8 years old and pregnant women. Azithromycin, cephalosporins, and amoxicillin are approved for use in children, and are FDA pregnancy category B drugs.[123]

Summary of the Evidence

Characteristics of included studies

The systematic search for children <8 years old identified 124 reports from databases and registers, and two from citation search; after screening for relevance, two reports were retrieved and included in the review. For pregnant women, the systematic search identified 21 reports from databases and registers and 1 report from citation search. After screening for relevance, four studies were retrieved and two were excluded since no prophylactic drug was included. There were 2 studies for pregnant women that were included in the review.

We identified two retrospective single cohort studies conducted in Mumbai, India[124] and Guyana[125] that reported on the outcomes of leptospirosis chemoprophylaxis programs implemented after flooding events. The study from India included 4,465 children under 8 years old and 359 pregnant women from a total sample of 156,934 individuals given prophylaxis. The study from Guyana involved an estimated 300,000 persons exposed to flood waters, including children <8 years old and pregnant women, but was not able to specify the actual numbers for these subgroups.

The study from Mumbai (Supe 2018) used azithromycin with a dosing regimen based on exposure risk.[124] One-time wading in contaminated water without open skin lesions were classified as low-risk exposure and were given a single dose within 24–72 h (children: 200 mg syrup or 250 mg tablet; pregnant women: 500 mg tablet). Those who waded on flood waters with open lesions or ingested contaminated water were classified as having moderate-risk exposure and received the same dose of azithromycin for 3 days. Other preventive measures were taken, including (1) special medical camps, (2) extensive public communication campaigns about doses of drugs to be followed, (3) advertisements for leptospirosis awareness, and (4) short text messages.

The study from Guyana (Dechet 2012) used a weekly 5-day course of amoxicillin in children <8 years old and pregnant patients exposed to flood waters.[125] Amoxicillin was available only in hospitals and health centers. Both studies did not have a control group.

The outcome measured by both studies was the incidence of leptospirosis following the flooding incident. The study from Mumbai identified PCR-confirmed leptospirosis, whereas the Guyana study included all suspected leptospirosis where not all reported cases were confirmed using *Leptospira* microscopic agglutination test (MAT). Both PCR and the 4-fold or greater increase *Leptospira* MAT are accepted confirmatory tests as defined by the United States CDC.[126]

Outcome measures assessed during the 12-week prophylaxis period included clinical symptoms (fever, body pain, red eye, calf pain, icterus) and laboratory markers for leptospirosis (IgG at 0, 6, and 12 weeks; IgM at 2nd week after disease onset).

Efficacy outcomes: Azithromycin vs. no prophylaxis (1 observational, very low certainty)

Incidence of leptospirosis

The number of laboratory-confirmed (i.e., PCR) leptospirosis cases specific to children or pregnant women were not reported. However, the total number of PCR-confirmed cases for the whole population of Mumbai, including those who received chemoprophylaxis, was 59, which is lower compared to the 432 leptospirosis cases recorded after a different flooding incident in the same region in 2005 without any public health intervention or chemoprophylaxis.[124] A worst-case scenario estimate of leptospirosis incidence during the 3 weeks after the flooding (the population receiving chemoprophylaxis used as denominator) is estimated at 38 cases per 100,000 population. No published outbreak-related incidence for Mumbai is published, but other studies report incidence rates of over 200 cases per 100,000 population during the 6 weeks after the 1996 flooding-related leptospirosis outbreak without public health intervention at Rio de Janiero.[127]

Safety outcomes: Azithromycin vs. no prophylaxis (1 observational, very low certainty)

Adverse events

Adverse events associated with chemoprophylaxis were not reported in this study.

Efficacy outcomes: Amoxicillin vs. no prophylaxis (1 observational, very low certainty)

Incidence of leptospirosis

Following the flooding incident, 236 suspected leptospirosis were reported in Guyana (general population, including those who received amoxicillin, and those who did not).[125] Among these, only 105 were tested using IgM ELISA with 2 confirmed and 53 probable leptospirosis cases. The worst-case scenario estimate for leptospirosis incidence for this report is estimated at 78 suspected leptospirosis cases per 100,000 population during the 6 weeks

after the flooding. No published outbreak-related incidence for Guyana is published, but other studies report incidence rates of over 200 cases per 100,000 population after the 1996 flooding-related leptospirosis outbreak without public health intervention in Rio de Janeiro.[127]

Safety outcomes: Amoxicillin vs. no prophylaxis (1 observational, very low certainty)

Adverse events

Adverse events associated with chemoprophylaxis were not reported in this study.

Efficacy and safety outcomes: Cephalosporin vs. no prophylaxis

No research evidence was identified for the effectiveness and safety of cephalosporin as leptospirosis prophylaxis for children <8 years of age and pregnant women.

GRADE summary of findings table

Table 20 shows the efficacy and safety outcomes in azithromycin or amoxicillin vs. no prophylaxis for leptospirosis in children and pregnant women.

Table 20. Azithromycin or amoxicillin compared to no prophylaxis for leptospirosis in children <8 years of age and pregnant women.

Outcomes	Basis (№ and type of studies, total participants)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty of Evidence
			Without prophylaxis	With prophylaxis	Difference	
Azithromycin (200/250mg OD for 1-3 days in children <8yo, 500 mg OD for 1-3 days in pregnant)						
Incidence of leptospirosis Assessed *via*: PCR	1 non-randomized study (N = 359 pregnant women, 4,465 children <8 years)	N/A	**432 cases** recorded after a different flooding incident in the same region in 2005 without any public health intervention or chemoprophylaxis	**59 cases** (~38 per 100,000)	Cannot be calculated	⨁◯◯◯ Very low[a,b]
Adverse events	1 non-randomized study (N = 359 pregnant women, 4,465 children)	Not reported	N/A	N/A	N/A	N/A
Amoxicillin (5 day course, dose unspecified)						
Incidence of leptospirosis Assessed *via*: Clinical findings, or IgM ELISA, or *Leptospira* MAT	1 non-randomized study (no. of pregnant women and children unreported)	N/A	N/A[e]	**236 suspected cases** (~78 per 100,000)	Cannot be calculated	⨁◯◯◯ Very low[c,d]
Adverse events	1 non-randomized study (no. of pregnant women and children unreported)	Not reported	N/A	N/A	N/A	N/A

a Extremely serious risk of bias: No adjustment for confounders done and the method for measuring the outcome is inappropriate (measured outcome is not limited to the study population, no stratification done).

b Very serious indirectness: The outcome reported was leptospirosis incidence in the whole of Mumbai who were given prophylaxis (N = 156,934) and not restricted to the study population and was not stratified for children or pregnant women.
c Extremely serious risk of bias: No adjustment for confounders done and the method for measuring the outcome is inappropriate (measured outcome is not limited to the study population, no was stratification done).
d Very serious indirectness: The outcome reported was leptospirosis incidence in Guyana, not restricted to the study population and was not stratified for children or pregnant women. Among the suspected leptospirosis cases, only 105 were tested using IgM ELISA, among them were 2 confirmed leptospirosis cases based on 4-fold increase in Leptospira MAT titers, 53 probable and 50 suspected leptospirosis cases.
e No outbreak-related incidence for Guyana is published, but other studies report incidence rates of over 200 cases per 100,000 population after the 1996 flooding-related leptospirosis outbreak without public health intervention in Rio de Janeiro.

Certainty of the Evidence

The overall certainty of evidence is **very low** for all outcomes reported.

The two studies had a very serious risk of bias due to study design limitations, no method to control for confounders, and no specific outcomes reported for pregnant women and children. The certainty of evidence was further downgraded for serious indirectness as it was impossible to identify which of the reported cases occurred in the population of interest or were associated with the prophylactic drugs.

Other Considerations

Resource implications (Cost/cost-effectiveness)

Table 21 shows the estimated ranges of azithromycin and amoxicillin based on the 2024 DPRI of the DOH.[115]

A cost-effectiveness study was done to compare prophylactic versus conventional treatment for leptospirosis through decision models and using United States and Barbados pricing.[116] The study found that in the United States, prophylaxis with azithromycin costs US$15.04 (₱842.24) per patient achieving 100% effectiveness, compared to $107.45 (₱6,017.20) per patient with no prophylaxis at a slightly lower effectiveness of 99.7%. No local cost-effectiveness studies were identified.

Table 21. Antibiotics for use in children and pregnant women, and their local unit cost estimates based on the 2024 DPRI[115] Price Range (₱).

Drug Name	Formulation	DPRI Unit Price (₱)		Average Prophylaxis Course Cost
		Lowest	Highest	
Children				
Azithromycin	200mg/5mL (15mL suspension) 200 mg/5mL (60mL suspension)	55.00 118.00	386.60 138.00	220.80 128.00
Amoxicillin	250mg/5mL (60mL suspension) 50mg/kg/day every 8 hours for 5 days	7.60	180.00	187.60 for a 20-kg child
Pregnant Women				
Azithromycin	500 mg tablet for 1 day 500 mg tablet for 3 days	3.60 3.60	101.64 101.64	52.62 157.86
Amoxicillin	500 mg capsule for 5 days	1.19	6.00	17.98

Stakeholder values, preferences, and acceptability

No research evidence identified.

Equity and feasibility

No research evidence identified.

Guideline Question 6.
Steroids, Cyclophosphamide, or Combination for Severe Leptospirosis

Should steroid, cyclophosphamide, or combination of both be used to prevent pulmonary hemorrhage and acute kidney injury in cases of severe leptospirosis?

Recommendation 6.
We suggest against the use of prednisolone to prevent pulmonary hemorrhage and acute kidney injury for cases of severe leptospirosis.

Certainty of evidence:	Very Low
Strength of recommendation:	Weak

Guideline Panel Considerations

The GP suggests against the use of prednisolone for the prevention of pulmonary hemorrhage and acute kidney injury in severe leptospirosis based on very low certainty of evidence. The available data demonstrated no clear benefit of prednisolone in reducing these complications. Furthermore, no safety data were reported.

No evidence was identified for other steroids or cyclophosphamide, resulting in substantial uncertainty regarding their potential benefits or harms. Therefore, no recommendation was made regarding their use in the prevention of pulmonary hemorrhage and acute kidney injury in cases of severe leptospirosis.

The panel emphasized that most available studies focus on treatment rather than prevention of these severe complications. In addition, local guidelines (PhilHealth Policy Recommendations)[128] already classify moderate to severe leptospirosis as involving pulmonary hemorrhage or renal failure, indicating that prevention may be challenging to apply in these settings.

Equity concerns were raised regarding the feasibility of implementing steroid or cyclophosphamide interventions, which would require tertiary hospital care, potentially disadvantaging low-resource settings and further limiting accessibility. Considering the lack of proven benefit, potential resource constraints, and uncertainty around safety, the panel agreed on a weak recommendation against the use of prednisolone for this indication.

Key Findings

- One RCT involving a total of 56 patients with leptospirosis assessed the efficacy of prednisolone in preventing pulmonary hemorrhage and acute kidney injury.
- Prednisolone, when compared to standard antibiotic therapy, demonstrated no significant benefit in preventing either pulmonary hemorrhage or acute kidney injury. However, there were no studies found for prednisolone regarding safety outcomes.
- The RCT demonstrated some concerns in the randomization process. Additionally, concerns regarding indirectness and imprecision were identified. These methodological limitations collectively contributed to downgrading the quality of evidence to low certainty.
- There were no studies reporting efficacy and safety outcomes for other types of steroids and cyclophosphamide found. This contributed to very low overall certainty of evidence.

Background

Steroids are primarily anti-inflammatory agents indicated in a variety of disease processes. They act on the inhibition of the production and activity of the majority of inflammatory cells, leading to the decrease in the inflammation.[129,130] Cyclophosphamide is an antineoplastic agent primarily indicated for malignant lymphomas. They act as an alkylating agent that forms cross-linkages within and between adjacent DNA strands, leading to apoptosis. They also have an immunosuppressive effects, particularly to T cells, leading to decreased secretion of interferon-gamma and cytokines.[131]

In severe leptospirosis, there is dysregulation of inflammatory responses that can trigger cytokine storm, leading to multi-organ failures, which includes pulmonary hemorrhage and acute kidney injury.[132] It is hypothesized that the anti-inflammatory and immunosuppressive effects of steroids and cyclophosphamide will help prevent pulmonary hemorrhage and acute kidney injury. However, currently there is no consensus on their use for this purpose as demonstrated by the lack of recommendations in the Philippine CPG for Leptospirosis 2010 and CPG on Leptospirosis for Children 2019.[133,134] Likewise, the WHO, Infectious Diseases Society of America (IDSA), and other major guideline-issuing bodies have not issued formal recommendations supporting the routine use of these immunosuppressive agents in leptospirosis management. While some clinicians may consider steroids in severe pulmonary cases based on limited evidence and case reports, this remains an area of clinical judgment rather than guideline-directed therapy. Cyclophosphamide use is even less supported in the literature and clinical practice.

Summary of the Evidence

Characteristics of included study

A study done in Iran (Alian 2014) between 2011 to 2013 focused specifically on patients with moderate to severe thrombocytopenia due to leptospirosis without specifying the severity of the disease.[135] The intention of the oral prednisolone regimen, 1 mg/kg/day for maximum of 7 days, was to address the thrombocytopenia, but with findings on the following composite outcomes as surrogate markers for organ-specific complications: azotemia and oliguria as a surrogate for acute kidney injury, and hemoptysis and tachypnea as a surrogate for pulmonary hemorrhage. The intervention of interest was compared with standard antibiotic care, ceftriaxone 1 g intravenously daily.

Efficacy outcomes: Prednisolone (1 RCT, N = 56, low certainty)

Pulmonary hemorrhage

In patients with leptospirosis and moderate to severe thrombocytopenia, adding oral prednisolone to standard care probably **does not reduce the risk of pulmonary hemorrhage**, measured using a composite surrogate outcome of hemoptysis and tachypnea, compared to standard care alone (low certainty of evidence). The incidence was similar between groups (with prednisolone 17.9% [5/28] vs. standard care alone 21.4% [6/28]; RR 0.83, 95% CI 0.29 –2.24).

Acute kidney injury

In patients with leptospirosis and moderate to severe thrombocytopenia, adding oral prednisolone to standard care probably **does not reduce the risk of acute kidney injury**, measured using a composite surrogate outcome of azotemia and oliguria, compared to standard care alone (low certainty of evidence). The incidence was similar between groups (with prednisolone 17.9% [5/28] vs standard care alone 17.9% [5/28]; RR 1.00, 95% CI 0.33–3.08).[135]

Safety outcomes: Prednisolone

No data on safety were reported.

Efficacy and safety outcomes: Other steroids

There were no studies found that investigated the effectiveness of other types of steroids in prevention of pulmonary hemorrhage and acute kidney injury.

Efficacy and safety outcomes: Cyclophosphamide

There were no studies found that investigated the effectiveness of cyclophosphamide in prevention of pulmonary hemorrhage and acute kidney injury.

GRADE summary of findings table

Table 22 shows the efficacy and safety outcomes in steroids vs. standard care for patients with severe leptospirosis.

Table 22. Steroids compared to standard care for patients with severe leptospirosis.

Outcomes	Basis (№ and type of studies, total participants)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty of Evidence
			Standard care	Steroids	Difference	
Efficacy outcomes						
Pulmonary hemorrhage	1 RCT (N = 56)	**RR 0.83** (0.29–2.41)	21.4%	**17.8%** (6.2–51.6)	**3.6% fewer** (15.2 fewer to 30.2 more)	⨁⨁◯◯ Low[a,b]
Acute kidney injury	1 RCT (N = 56)	**RR 1.00** (0.33–3.08)	17.9%	**17.9%** (5.9–55)	**0.0% fewer** (12 fewer to 37.1 more)	⨁⨁◯◯ Low[a,b]
Safety outcomes - not reported						

a The severity of leptospirosis was not described.
b Imprecision due to wide confidence intervals.

Certainty of the Evidence

For efficacy of prednisolone in preventing pulmonary hemorrhage and acute kidney injury, the certainty of evidence is **low** due to serious indirectness (unclear description of leptospirosis severity) and imprecision. For safety of prednisolone, the certainty of evidence is **very low** as no studies reported on this outcome.

Other Considerations

Resource implications (Cost/cost-effectiveness)

Oral prednisolone is not listed in the 2024 DPRI of the DOH.[115] Data from the website of Southstar suggests that the costs of the described oral prednisolone regimen is ₱168.00 (Table 23).[136]

No cost-effectiveness studies were identified.

Table 23. Cost of prednisolone in the current Philippine market (₱).

Drug Name	Formulation	Unit Price (₱)	Estimated Cost of Treatment (₱)
Prednisolone	30 mg tablet	12.00	168.00 for a 60 kg adult

Stakeholder values, preferences, and acceptability

No research evidence identified.

Equity and feasibility

No research evidence identified.

Guideline Question 7.
Acellular Pertussis Vaccines

Should acellular pertussis (aP) vaccines be used instead of whole cell pertussis (wP) vaccines to prevent pertussis in infants?

Recommendation 7.
We recommend the use of acellular OR whole cell pertussis vaccines to prevent pertussis in infants.

Certainty of evidence:	Low
Strength of recommendation:	Strong

Guideline Panel Considerations

Despite the superior safety and tolerability profile of aP vaccines, the GP issued a strong recommendation for the use of either acellular OR whole-cell pertussis vaccines to prevent pertussis in infants. This decision was informed by the following considerations:

First, available evidence suggests comparable clinical efficacy between aP and wP vaccines in preventing confirmed pertussis infection, with the observed higher antibody titers associated with aP vaccines not definitively translating to improved real-world protection.

Second, substantial concerns regarding cost and health equity influenced the panel's deliberations. aP vaccines are significantly more expensive, raising the risk of limited access for low-income and rural populations if only aP vaccines are recommended, especially in settings where vaccines are not universally provided for free through the National Immunization Program.

Third, while parents may prefer aP vaccine due to fewer side effects, the GP acknowledged that affordability and trust in health workers could still drive acceptance of wP vaccine, highlighting the need to balance safety, cost, and accessibility in vaccine choice.

Given these programmatic and equity concerns, the GP opted to recommend either vaccine instead of recommending between the two pertussis vaccines. This recommendation to allow the use of either aP OR wP vaccines provides flexibility to national programs and healthcare providers, ensuring both protection against pertussis and equitable access to vaccination.

Key Findings

- Four RCTs (N = 76,804 infants) and 1 large observational study based on real-world data (N = 62,916,460 vaccines distributed/administered) investigated the effect of aP vaccines compared to wP vaccines as prevention of pertussis infection in infants.
- Based on 4 RCTs, aP vaccines resulted in little to no difference in efficacy compared to wP vaccines in terms of prevention of pertussis in infants. Three RCTs showed that aP vaccine results in higher antibody levels against pertussis antigen/s compared to wP vaccine.
- For adverse outcomes, an RCT showed that aP vaccines resulted in lower proportion of patients developing limpness, but little to no difference in proportion of patients developing serious adverse events in general, including death, death alone, seizures, hypotonic-hyporesponsive episodes, and generalized cyanosis. One observational study showed that aP vaccines probably results in lower proportion of patients developing seizures, neurological disabilities, infantile spasms,

encephalitis/encephalopathy, autism, speech disorders, life-threatening reactions, and seizures, needing emergency department visits and hospitalizations, and dying compared to wP vaccines, but probably results in little or no difference in proportion of patients developing sudden infant death syndrome and cerebellar ataxia compared to wP vaccine.

- Three of the RCTs had low risk of bias. One RCT had risk of bias issues due to some concerns in measurement of outcome and potential deviations in intended interventions.

Background

Pertussis is a respiratory infection caused by the bacterium *Bordetella pertussis*. It is highly contagious and can cause prolonged cough that may last up to months. Immunization with three doses of pertussis-containing vaccine is the most effective strategy to prevent and decrease the risk of severe illness.[137] In 2018, while 86% of the global target population received the recommended doses during infancy, there were more than 151,000 reported cases of pertussis.[137,138] In the Philippines, 568 cases and 40 deaths were reported in the most recent outbreak in March 2024.[139]

There are two types of pertussis vaccines: whole-cell and acellular vaccines. Whole-cell vaccines are based on killed *B. pertussis* organisms, containing 3,000 different proteins, and are frequently associated with minor local and systemic adverse reactions (1 in 2–10 vaccinations), and uncommonly associated with severe systemic reactions, such as hypotonic-hyporesponsive episodes (HHE) (<1 in 1,000–2,000 vaccinations). The second type of pertussis vaccine is the aP vaccine, which contains only one or more highly purified individual pertussis antigens. It has, in many countries, replaced the wP vaccine as early as 1981 to decrease the reactogenicity of the vaccine.[140]

Summary of the Evidence

Characteristics of included studies

Four RCTs (N = 76,804) investigated the effect of aP vaccines compared to wP vaccines as prevention for pertussis infection for infants. Two RCT were performed in Italy (Greco 1996; Olin 1997),[141,142] one in Senegal (Simondon 1997),[143] and one in Sweden (Gustafsson 1996).[144] The three-dose primary vaccination protocols for the RCT followed its country recommendation for age and the vaccine brands used depended on what was available in the country. Confirmed pertussis was defined by 21 days or more of paroxysmal cough, with infection confirmed by culture or serologic testing. Whole cell pertussis vaccine was used as a comparator across all four studies. Follow up for adverse outcomes ranged from six months to two years from the receipt of the first dose of vaccine.

One observational study (Geier 2004; retrospective cohort, N = 62,916,460 vaccines distributed/administered) based on real-world data collected from the CDC Vaccine Adverse Event Reporting System evaluated neurological disorders following vaccination with acellular and wP vaccines.[145]

Efficacy outcomes

Confirmed pertussis (4 RCTs, N = 76,804 infants, moderate certainty)

Based on four RCTs (N = 76,804), aP vaccine **probably results in little or no difference in proportion of patients developing confirmed pertussis** compared to wP vaccine (RR 0.70, 95% CI 0.31–1.58).

Immunogenicity (3 RCTs, N = 2,568, moderate certainty)

Three RCTs reported on immunogenicity of aP vaccines compared to wP in infants which showed that aP vaccine probably results in higher antibody levels against pertussis antigen/s compared to wP vaccine.

One RCT (N = 689 infants) showed that post-vaccination antibody levels against pertussis toxin, filamentous hemagglutinin, fimbriae types 2 and 3, and pertactin after 5-component aP vaccine were higher compared to that measured after wP vaccine.[144]

One RCT (N = 307) showed that the recipients of acellular vaccines had high concentrations of antibodies to pertussis toxin, especially in the 3-component-vaccine group (median 158 U/mL) compared to that of the wP vaccine group (median 11 U/mL). Concentrations of IgG antibodies to filamentous haemagglutinin were highest in the 2-component-vaccine group and lowest in the 3-component-vaccine group. Pertactin antibody concentrations were similar for the three vaccines that contained pertactin, whereas the anti-fimbriae concentrations were higher for the wP vaccine group than for the five-component-vaccine group.[142]

One RCT (N = 1,572 infants) showed that two acellular vaccines (brands: Biocine and SmithKline aP vaccines) elicited significantly higher titers of IgG (51.3 and 94.4 vs. 1.2 geometric mean titer, $p < 0.001$) and neutralizing antibody to pertussis toxin 230.0 and 787.6 vs. 23.0 geometric mean titer, $p < 0.001$), filamentous hemagglutinin (147.0 and 52.6 vs. 5.2 geometric mean titer, $p < 0.001$), and pertactin (274.2 and 136.6 vs. 37.9 geometric mean titer, $p < 0.001$) than did the whole-cell vaccine.[141]

Safety outcomes

Serious adverse events, including death (1 RCT, N = 81,835 doses, high certainty)

One RCT (N = 81,835) reported on serious adverse events, including HHE, severe allergic reactions, acute neurological disorders, invasive bacterial infections, other life-threatening conditions, and death, which showed that aP vaccine **results in little to no difference in proportion of patients developing serious adverse events, including death** (RR 0.68, 95% CI 0.50–0.92) compared to wP vaccine.

Emergency department visits (1 Cohort, N = 62,916,270, low certainty)

Based on one cohort study (N = 62,916,270), aP vaccine **probably results in lower proportion of patients needing** emergency department visits (RR 0.44, 95% CI 0.41–0.48) compared to wP vaccine.

Life-threatening reactions (1 Cohort, N = 62,916,270, low certainty)

Based on one cohort study (N = 62,916,270), aP vaccine **probably results in lower proportion of patients developing** life-threatening reactions (RR 0.40, 95% CI 0.25–0.64) compared to wP vaccine.

Hospitalizations (1 Cohort, N = 62,916,270, low certainty)

Based on one cohort study (N = 62,916,270), aP vaccine **probably results in lower proportion of patients needing** hospitalizations (RR 0.39, 95% CI 0.32–0.47) compared to wP vaccine.

Death (1 RCT, N = 81,835 doses, moderate certainty; 1 Cohort, N = 62,916,270, low certainty)

Based on one RCT (N = 81,835), aP vaccine **probably results in little to no difference compared to wP vaccine in proportion of patients dying** (RR 0.90, 95% CI 0.47–1.70). However, one cohort showed that aP vaccine **probably results in lower proportion of patients dying** (RR 0.55, 95% CI 0.36–0.85) compared to wP vaccine.

Seizures (2 RCTs, N = 54,470 doses, moderate certainty; 1 Cohort, N = 62,916,270, low certainty)

Two RCTs (N = 54,470) reported seizures and showed that aP vaccine **probably results in little to no difference in proportion of patients developing seizures compared to wP vaccines** (RR 0.43, 95% CI 0.11–1.75), while one cohort showed that aP vaccine **probably results in lower proportion patients developing seizures** compared to wP vaccine (RR 0.27, 95% CI 0.22–0.23).

Neurological disabilities (1 Cohort, N = 62,916,270, low certainty)

One cohort showed that aP vaccine **probably results in lower proportion of patients developing neurological disabilities** compared to wP vaccine (RR 0.26, 95% CI 0.13–0.51).

Infantile spasms (1 Cohort, N = 62,916,270, low certainty)

One cohort showed that aP vaccine **probably results in lower proportion of patients developing infantile spasms** compared to wP vaccine (RR 0.24, 95% CI 0.07–0.77).

Encephalitis/encephalopathy (1 Cohort, N = 62,916,270, low certainty)
One cohort showed that aP vaccine **probably results in lower proportion of patients developing encephalitis/encephalopathy** compared to wP vaccine (RR 0.11, 95% CI 0.04–0.33).

Autism (1 Cohort, N = 62,916,270, low certainty)
One cohort showed that aP vaccine **probably results in lower proportion of patients developing autism** compared to wP vaccine (RR 0.20, 95% CI 0.06–0.61).

Speech disorders (1 Cohort, N = 62,916,270, low certainty)
One cohort study showed that aP vaccine **probably results in lower proportion of patients developing speech disorders** compared to wP vaccine (RR 0.28, 95% CI 0.12-0.66).

Sudden Infant Death Syndrome (SIDS) (1 Cohort, N = 62,916,270, low certainty)
One cohort study showed that aP vaccine **probably results in little or no difference in proportion of patients developing SIDS** compared to wP vaccine (RR 0.56, 95% CI 0.32–1.00).

Cerebellar ataxia (1 Cohort, N = 62,916,270, low certainty)
One cohort showed that aP vaccine **probably results in little or no difference in proportion of patients developing cerebellar ataxia** compared to wP vaccine (RR 0.98, 95% CI 0.28–3.39).

Hypotonic-hyporesponsive episodes (3 RCTs, N = 136,305 doses, moderate certainty)
Based on three RCTs (N = 136,305), aP vaccine **probably results in little to no difference in proportion of patients developing hypotonic-hyporesponsive episodes** compared to wP vaccine (RR 0.23, 95% CI 0.02–2.59).

Systemic reactions: Generalized cyanosis (1 RCT, N = 40,994 doses, moderate certainty)
Based on one RCT (N = 40,994), aP vaccine **probably results in little to no difference in proportion of patients developing generalized cyanosis** compared to wP vaccine (RR 0.10, 95% CI 0.00–2.05).

Systemic reactions: Limpness (1 RCT, N = 6,906 doses, high certainty)
Based on one RCT (N = 6,906), aP vaccine **results in lower proportion of patients developing limpness** compared to wP vaccine (RR 0.09, 95% CI 0.06–0.16).

Other outcomes (Important but not rated critical for decision-making)

Fever
Based on one RCT (N = 40,994, high certainty), aP vaccine **results in lower proportion of patients developing fever ≥40°C** (RR 0.14, 95% CI 0.07–0.29) compared to wP vaccine, while based on two RCTs (N = 47,900, moderate certainty), aP vaccine **probably results in lower proportion of patients developing fever ≥38°C** (RR 0.12, 95% CI 0.09–0.16) compared to wP vaccine.

Persistent crying
Based on two RCTs (N = 54,470, high certainty), aP vaccine **results in lower proportion of patients developing persistent crying 3 hours** (RR 0.13, 95% CI 0.07–0.23), and based on one RCT (N = 6,906, high certainty), aP vaccine **results in lower proportion of patients developing persistent crying ≥1 hour** (RR 0.14, 95% CI 0.11–0.18) compared to wP vaccine.

Unusual cry and pallor (1 RCT, N = 6,906 doses, high certainty)
Based on one RCT (N = 6,906), aP vaccine **results in lower proportion of patients developing unusual cry** (RR 0.12, 95% CI 0.10–0.13) and **pallor** (RR 0.08, 95% CI 0.05–0.14) compared to wP vaccine.

Redness ≥2cm and Nodule ≥2cm (1 RCT, N = 6,906 doses, high certainty)
Based on one RCT (N = 6,906), aP vaccine **results in lower proportion of patients developing redness ≥2 cm** (RR 0.05, 95% CI 0.03–0.09) and **nodule ≥2 cm** (RR 0.06, 95% CI 0.04–0.08) compared to wP vaccine.

Local swelling and irritability (1 RCT, N = 40,994 doses, high certainty)
Based on one RCT (N = 40,994), aP vaccine **results in lower proportion of patients developing local swelling** (RR 0.31, 95% CI 0.29–0.32) and **irritability** (RR 0.61, 95% CI 0.59–0.62) compared to wP vaccine.

Local tenderness (2 RCTs, N = 47,900 doses, moderate certainty)
Based on two RCTs (N = 47,900), aP vaccine **probably results in lower proportion of patients developing local tenderness** (RR 0.14, 95% CI 0.13–0.16) compared to wP vaccine.

GRADE summary of findings table

Table 24 shows the efficacy and safety outcomes in aP vs. wP vaccines for infants.

Table 24. Acellular pertussis vaccine compared to whole cell pertussis vaccine in infants.

Outcomes	Basis (№ and type of studies, total participants)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty of Evidence
			wP	aP	Difference	
Efficacy outcomes						
Confirmed pertussis Assessed *via*: 21 days or more of paroxysmal cough, confirmed by culture, or serologic testing Follow-up: range 6 months to 23.5 months	4 RCTs (N = 76,804)	**RR 0.70** (0.31–1.58)	1.7%	**1.2%** (0.5–2.6)	**0.5% fewer** (from 1.2 fewer to 1 more)	⊕⊕⊕◯ Moderate[a]
Immunogenicity Assessed *via*: Antibody levels Follow-up: mean 1 month	• In 1 RCT (N = 689), a 5-component aP vaccine induced higher antibody responses to pertussis toxin, filamentous hemagglutinin, fimbriae 2/3, and pertactin than wP. • Another trial (N = 307) reported a median pertussis toxin antibody level of 158 U/mL in the 3-component aP group versus 11 U/mL in the wP group. • A larger study (N = 1,572) showed significantly higher geometric mean titers for aP vaccines across multiple antigens—for example, pertussis toxin neutralizing antibody levels were 230.0 and 787.6 in aP groups versus 23.0 in the wP group ($p <$ 0.001).					⊕⊕⊕⊕ High
Safety outcomes						
Serious adverse events (HHE, severe allergic reactions, acute neurological disorders, invasive bacterial infections, other life-threatening conditions), including death Assessed *via*: physician	1 RCT (N = 81,835)	**RR 0.68** (0.50–0.92)	0.3%	**0.2%** (0.1–0.3)	**0.1% fewer** (0.1 fewer to 0 fewer)	⊕⊕⊕⊕ High

Outcomes	Basis (№ and type of studies, total participants)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty of Evidence
			wP	aP	Difference	
assessment Follow-up: range 1 day to 6 months						
Death Assessed *via*: physician assessment Follow-up: range 1 day to 6 months	1 RCT (N = 81,835)	**RR 0.90** (0.48–1.70)	0.1%	**0.1%** (0–0.1)	**0.0% fewer** (0 fewer to 0 fewer)	⊕⊕⊕◯ Moderate[a]
Hypotonic, hyporesponsive episodes Assessed *via*: patient report and physician assessment Follow-up: range 1 day to 6 months	3 RCTs (N = 136,305)	**RR 0.23** (0.02–2.59)	0.1%	**0.0%** (0–0.3)	**0.1% fewer** (0.1 fewer to 0.2 more)	⊕⊕⊕◯ Moderate[a]
Seizures Assessed *via*: patient report and physician assessment Follow-up: range 1 day to 6 months	2 RCTs (N = 54,470)	**RR 0.43** (0.11–1.67)	0.0%	**0.0%** (0–0)	**0.0% fewer** (0 fewer to 0 fewer)	⊕⊕⊕◯ Moderate[b]
Generalized cyanosis Assessed *via*: patient report and physician assessment Follow-up: range 1 day to 8 days	1 RCT (N = 40,994)	**RR 0.10** (0–2.05)	0.0%	**0.0%** (0–0)	**0.0% fewer** (0 fewer to 0 fewer)	⊕⊕⊕◯ Moderate[b]
Limpness Assessed *via*: patient report and physician assessment Follow-up: range 1 day to 14 days	1 RCT (N = 6,906)	**RR 0.10** (0.06–0.15)	5.1%	**0.5%** (0.3–0.8)	**4.6% fewer** (4.8 fewer to 4.4 fewer)	⊕⊕⊕⊕ High

a Significant heterogeneity
b Few events resulting in wide confidence interval

Certainty of the Evidence

Three of the RCTs had low risk of bias.[141,142,144] One RCT had risk of bias issues due to some concerns in measurement of outcome and potential deviations in intended interventions.[143] Overall certainty for the effectiveness outcomes was downgraded to moderate due to imprecision, while overall certainty for adverse reactions was low.

Other Considerations

Cost of vaccination

As shown in Table 25, acellular pertussis vaccines cost between ₱980 to ₱2,633 depending on the brand. Adding the cost of multiple clinic visits, the total cost of aP vaccination may range between ₱17,500 to ₱25,000. On the other hand, wP vaccines are available at health centers for free. Table 24 shows the price comparison between the two vaccines.

Table 25. Price of acellular and whole cell pertussis vaccines.

Vaccine type	Particulars	Vaccine Cost per dose[a] (₱)	Average Clinic Price[a] (₱)	Regimen for primary doses[c]	Total Cost (₱)
Acellular	DTaP-IPV-Hep B-Hib (Hexaxim, Infarixhexa) starting 6 wks old	2,633.00[136]	5,000.00	3 primary doses, 2 boosters for a child up to 6 years old	15,000.00
	DTaP-IPV-Hib (Pentaxim, Infanrix) starting 6 wks old	2,633.00[136]	4,500.00	3 primary doses, 2 boosters for a child up to 6 years old	13,500.00
Whole cell	DTwP-Hib-Hep B (0.5 mL suspension vial per dose)	90.00[115]	N/A	3 primary doses for a child less than 1 year old[b]	0

[a] Unit prices reflect vaccine cost from suppliers. Estimated average clinic price is the cost of the vaccine when administered by the physician (per dose).
[b] This regimen is provided for free at local health centers as part of the Expanded Program on Immunization (EPI).[147]
[c] Two booster doses at 12 to 18 months, and at 4 to 6 years of age are indicated in the Childhood Immunization Schedule,[148] both of which are not covered by the EPI.

Cost-effectiveness

No local cost-effectiveness studies were identified.

A 2010 Canadian study looked at the economic impact of replacing the wP vaccine with an acellular vaccine and found that it resulted in an incremental cost of C$108 (₱4,320) for each pertussis case avoided and savings of C$184 (₱7,360) per pertussis case avoided. It concluded that switching to aP vaccines was "cost-saving from the societal perspective and cost-effective from the Ministry of Health perspective."[149]

Stakeholder values, preferences, and acceptability

No local research evidence was identified.

A comparative study done in Canada in 1998 on preferences of 400 mothers of 1-month-old infants, 100 immunizing physicians, and 100 immunizing nurses for use of a new generic aP vaccine which is less reactogenic than wP vaccine but is as effective, but which would require multiple injections to deliver all other recommended vaccines.[150] More mothers were concerned by the common reactions caused by the wP vaccine (75.8% vs. 52%; p = 0.001) and prefer a less reactogenic vaccine product even if it requires multiple injections (57.3% vs. 29.5%). Health care professionals preferred wP vaccines and are more concerned about multiple injections (61.1% vs. 29.3%). These results must be interpreted cautiously as contextual factors may have been different at that time.

Equity and feasibility

Four RCTs studied the immunogenicity and safety of aP vaccines given in combination or co-administered with other vaccines to infants, the results of which may affect feasibility of administration of aP vaccine particularly in resource-limited areas. Two RCTs from China co-administered aP vaccine with Measles, Mumps, and Rubella vaccine (MMR) and inactivated poliovirus vaccine (IPV)[151] and aP vaccine with IPV,[152] and found that co-administration did not affect the immunogenicity and safety profile of the aP vaccines. Similarly, combining aP vaccines with IPV proved to have good immunogenicity and safety profile as well, based on two RCTs done in Russia[153] and Japan.[154] Mixing of acellular and whole pertussis vaccines used as primary series (1st dose acellular and subsequent doses wP) resulted in more reported adverse reactions based on an RCT done in Australia.[155]

Guideline Question 8.
Avian Influenza Diagnostics

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?

Recommendation 8.1.
We recommend the use of RT-PCR to confirm the diagnosis of avian influenza in suspected cases.

Certainty of evidence:	Very Low
Strength of recommendation:	Strong

Recommendation 8.2.
We recommend against the use of RAT to confirm the diagnosis of avian influenza in suspected cases.

Certainty of evidence:	Very Low
Strength of recommendation:	Strong

Guideline Panel Considerations

The GP issued a strong recommendation for the use of RT-PCR to confirm the diagnosis of avian influenza in suspected cases and a strong recommendation against the use of multiplex RAT for the same purpose.

The GP expressed significant concerns regarding the accuracy, accessibility, and feasibility of diagnostic tests for avian influenza, particularly in resource-limited settings. The panel stated that RT-PCR is widely recognized by the CDC as the reference standard for avian influenza diagnosis. However, the panel is concerned that while the RT-PCR offers high sensitivity and specificity, its reliance on laboratory infrastructure limits feasibility in rural areas, creating significant equity concerns for poultry workers and disadvantaged communities who may lack access. The panel also noted the limitations in current practice in the Philippines where RT-PCR can only detect the hemagglutinin subunit RNA and not the neuraminidase subunit RNA.

Members of the panel also noted the absence of direct evidence on clinical outcomes from either test, and the lack of studies on harms. Available evidence indicates that multiplex RAT has poor and inconsistent sensitivity, especially in specimens with lower viral loads. This raises substantial concerns regarding the risk of false-negative results, which the panel recognized as clinically significant, potentially leading to delayed diagnosis, inappropriate treatment, and uncontrolled disease spread in the community.

While the panel acknowledged the practical limitations of RT-PCR, including its reliance on laboratory infrastructure and reduced accessibility in rural or resource-limited settings, these were considered outweighed by the clinical and public health risks associated with inaccurate diagnosis. In addition, the lack of formal registration and regulatory approval for multiplex RAT in the Philippines represents a further barrier to its use in clinical practice. While RAT may be more cost-effective, their lower accuracy is a major trade-off, highlighting the challenge of balancing affordability with diagnostic reliability.

Although the overall certainty of evidence was very low due to the limited quantity and quality of available studies, the potential for significant patient and public health harm from false-negative RAT results justified strong recommendations. RT-PCR remains the recommended confirmatory diagnostic test for avian influenza in suspected cases, while the use of multiplex RAT is not recommended given its poor diagnostic performance, regulatory limitations, and potential to compromise clinical care and outbreak control efforts.

Key Findings

- Three observational studies included a total of 168 patients and 319 specimens. One case-control study assessed the sensitivity of two multiplex RAT brands for detecting A(H7N9) using throat swab specimens from patients who have tested positive based on real-time RT-PCR. No study compared multiplex RAT with viral isolation. Two studies compared RT-PCR with viral isolation but did not report diagnostic accuracy measures.
- The sensitivity of multiplex RAT with RT-PCR as the reference standard is poor; specificity, predictive values, diagnostic odds ratio (DOR) and area under the curve (AUC) cannot be calculated since only positivity rate was reported. Test sensitivity also varied across brands and viral load in the sample.
- No diagnostic accuracy measure was reported in any of the two studies comparing RT-PCR with viral isolation. RT-PCR has lower per patient cost than viral culture; no study investigated the cost-effectiveness of RT-PCR and viral culture. Likewise, data on either cost or cost-effectiveness of multiplex RAT are lacking.
- The overall certainty of evidence was very low.

Background

Human infection with avian influenza virus is rare but there is a setting for a possible future pandemic. Specific subtypes known to infect humans are H5N1, H7N3, H7N7, H7N9, H9N2, and H10N8; H5N1 and H7N9 are the most common ones.[156] H5N1 infects younger individuals while H7N9 affects older patients more.[157] Avian influenza virus can also be classified as high pathogenicity avian influenza (HPAI) and low pathogenicity avian influenza (LPAI) based on its ability to kill chickens in the laboratory setting.[156] The pooled global seroprevalence of highly pathogenic avian influenza A(H5N1) virus is 0.2% (95% CI 0.1–0.3%) among 22,920 participants.[3] Poultry exposure is the main risk factor; poultry workers (0.5%, 95% CI 0.3–0.7%), poultry cullers (0.4%, 95% CI 0–0.9%), and persons with poultry and human exposures (0.8%, 95% CI 0.2–1.4%) had relatively higher A(H5N1) virus antibody seroprevalence than those without poultry exposures.[13] It is also more prevalent in Southeast Asia, Africa, and Middle East because of increased human-poultry interactions.

Human infection with avian influenza virus is rare but there is a setting for a possible future pandemic. The pooled global seroprevalence of highly pathogenic avian influenza A(H5N1) virus is 0.2% (95% CI 0.1–0.3%) among 22,920 participants.[13] Poultry exposure is the main risk factor; poultry workers (0.5%, 95% CI 0.3–0.7%), poultry cullers (0.4%, 95% CI 0.0–0.9%), and persons with poultry and human exposures (0.8%, 95% CI 0.2–1.4%) had relatively higher A(H5N1) virus antibody seroprevalence than those without poultry exposures.[13]

WHO reported that from January 1, 2003 to April 22, 2025, there were 265 cases of human infection with avian influenza A(H5N1) virus reported from five countries within the Western Pacific Region, with 139 fatal cases or a CFR of 54.7%. No new case of human infection with avian influenza A(H5N1) virus was reported to WHO in the Western Pacific Region as of January 2024.[14] In the Philippines, although there is no report of human avian influenza, the Bureau of Animal Industry is reporting outbreaks of avian influenza A(H5N1) in some poultry farms. Three H5N1 outbreaks in chicken and ducks were reported in 2 districts in Pampanga from March 26 to April 4. The last outbreak was recorded on April 30; HPAI H5N9 was first detected in the Philippines, specifically in a duck farm in Camarines Sur.[158] These situations are settings for potential human infections.

Having an accurate diagnosis of avian influenza is necessary to guide definitive treatment especially in areas with limited resources, as well as to alert authorities regarding potential outbreaks. We aim to assess the diagnostic

performance of multiplex RAT and RT-PCR compared to viral isolation, as well as the diagnostic performance of multiplex RAT when RT-PCR is used as the reference standard.

Tests used to diagnose avian influenza include the following:

- **Reverse Transcription Polymerase Chain Reaction (RT-PCR):** detects viral RNA; can detect low levels of the virus, differentiate influenza subtypes (e.g., H5, H7); considered gold standard for laboratory confirmation
- **Multiplex Rapid Antigen Test (RAT):** detects viral proteins (i.e., antigens); fast results (15-30 min) and may be used at point of care but generally less sensitive than RT-PCR especially in cases with low viral loads
- **Virus isolation:** involving growing virus in eggs or cell culture; used for confirmation and research but slower
- **Serological tests (e.g., ELISA, hemagglutination inhibition):** detects antibodies to the virus; used for surveillance or confirming past infection
- **Immunofluorescence assay (IFA):** detects viral antigens in infected cells; requires specialized equipment

Summary of the Evidence

Characteristics of included study

Studies on multiplex RAT

Three observational studies including a total of 168 patients and 319 specimens were found. One was a case-control study from China (Chen 2015) comparing multiplex RAT with real-time RT-PCR as reference standard.[159] The study sample included 110 throat swab or sputum specimens from 53 A(H7N9)-infected patients. No study comparing multiplex RAT with viral isolation was found. Only the sensitivities of multiplex RAT, specifically Wondfo Flu A test, colloidal gold method, and Wondfo H7 Subtype test, colloidal gold method were calculated since only positivity rate was mentioned.

Studies on RT-PCR

Two studies compared RT-PCR with viral isolation; one case-control study from Korea (Choi 2013) tested 319 throat swab specimens.[160] However, data on H5N1 were excluded in the analysis. Another cohort study from Thailand (Apisarnthanarak 2006) sampled tracheal aspirates from 115 clinically suspected patients but only reported on the diagnostic costs per patient of RT-PCR for H5N1 and viral culture for each patient, obtained from line-item reports of the hospital's fiscal system.[161]

Diagnostic accuracy

Multiplex RAT

One case-control study reported the sensitivity of multiplex RAT with RT-PCR as the reference standard.[159] The pooled sensitivity of multiplex RAT is low (35.1%, 95% CI 13.0 to 66.2%). The heterogeneity was high (I^2 = 95%), with sensitivity varying across the two test brands evaluated: Wondfo H7 Subtype test at 50.9% (95% CI 41.6–60.1%) and Wondfo Flu A test at 21.8% (95% CI 15.1–30.5%). Sensitivity of multiplex RAT was 100% with high viral loads (i.e, Ct values <25), and decreased to 29 to 74% for Ct values = 25–30, and 24 to 32% if Ct >30. Specificity, predictive values, DOR and AUC cannot be calculated since only positivity rate was reported.

RT-PCR

No diagnostic accuracy measure was reported in any of the two studies comparing RT-PCR with viral isolation.

GRADE summary of findings table

Table 26 shows the diagnostic performance of multiplex RATs for avian influenza.

Table 26. Diagnostic performance of multiplex RATs for avian influenza.

Test results	Basis (№ and type of studies, total participants)	Number of results per 10,000 patients tested (95% CI)			Certainty of Evidence
		Prevalence 0% Typically seen in the general population	**Prevalence 0.6%**[a] Typically seen in poultry cullers or poultry workers	**Prevalence 1.8%**[b] Typically seen in individuals with both poultry and human exposures	
True positives	1 study (N = 220)	**0** (0–0)	**21** (8–40)	**63** (23–119)	⊕◯◯◯ **Very low**[c,d,e]
False negatives		**0** (0–0)	**39** (20–52)	**117** (61–157)	

a 0.6% was the estimated upper 95%CI for seroprevalence for poultry-exposed populations based on a systematic review of seroprevalence (N = 19,320).
b 1.8% was the estimated upper 95CI% for seroprevalence in persons exposed to both human A(H5N1) cases and infected birds based on a systematic review of seroprevalence (N = 19,320). Seroprevalence was higher in persons exposed to A(H5N1) clade 0 virus (1.9%, range 0.7–3.2%) than in participants exposed to other clades of A(H5N1) virus (range 0–0.5%) (p <0.05).
c Case-control design
d Sensitivity is significantly different across brands tested and viral load levels. Sensitivity was as 50.9% (41.6–60.1%) in Wondfo FH7; 21.8% (15.1–30.5%) in Wondfo Flu A test. Sensitivity was 100% in viral load if detected at Ct values <25, 29 to 74% if Ct = 25–30, and 24–32% if Ct > 30.
e Wide confidence intervals for sensitivity (13–66%). Throat swab specimens were collected and not sputum/tracheal samples.

Certainty of the Evidence

The overall certainty was very low for the sensitivity of multiplex RAT. Downgrading was done because of high risk of bias related to patient selection (i.e., use of a case-control design) and index test (i.e., PCR done before the index test). Serious inconsistency was also noted in the sensitivity results between the brands tested.

Other Considerations

Resource implications (cost/cost-effectiveness)

One cohort study from Thailand estimated that RT-PCR and viral culture in avian influenza (H5N1) screening cost around US$25 (₱1,400) and US$30 (₱1,680) per patient, respectively.[160] No study investigated the cost-effectiveness of RT-PCR over viral culture. Likewise, data on either cost or cost-effectiveness of multiplex RAT are lacking.

Stakeholder values, preferences, and acceptability

No study on stakeholder values, preferences, and acceptability was found regarding avian influenza testing.

Increasing awareness of avian influenza may be necessary especially for individuals with high probability of exposure. A 2006 study compared the effectiveness of lectures and flyers in improving knowledge, attitudes, and practices about avian influenza among poultry handlers in Zamboanga City.[162] Results showed that while both methods were effective, lectures were significantly better at improving knowledge, whereas both were equally effective in enhancing attitudes and practices.

Equity and feasibility

No study on equity and feasibility was found. Based on the Philippine FDA Verification Portal as of June 15, 2025, all RATs evaluated in the study by Chen *et al.*[159] (i.e., Wondfo FluA and H7 tests) are not currently registered.

The published proceedings from the DOH National Center for Disease Prevention and Control in 2006 emphasized key strategies for avian influenza prevention and control: early identification and reporting of the virus in birds to minimize human exposure, and prompt detection and isolation of human cases to control spread within communities.[163] Another article highlighted the role of family physicians in the initial diagnosis of avian influenza based on clinical manifestations and the triage of suspected cases using epidemiological risk factors due to the limited availability and high cost of laboratory testing in many hospitals.[164]

Guideline Question 9.
Mpox Quarantine

Should quarantine be recommended for close contacts of confirmed or suspected cases of mpox?

Recommendation 9.1.
We suggest against mandatory quarantine for close contacts* of confirmed or suspected cases of mpox.

Certainty of evidence: Very Low
Strength of recommendation: Weak

* *WHO definition of close contact (Aug 26, 2024)*[165]

Recommendation 9.2 (Good Practice Statement*).
For close contacts** of suspected or confirmed cases of mpox, we suggest active surveillance of symptoms and avoid direct interaction with immunocompromised individuals*** for 21 days post-exposure.

Certainty of evidence: None
Strength of recommendation: N/A

* *This Good Practice Statement is based on expert consensus intended to support best practice but is not a mandatory recommendation.*
** *WHO definition of close contact (Aug 26, 2024)*[165]
*** *CDC definition (Sep 13, 2024)*[166]

Recommendation 9.3 (Good Practice Statement*).
We suggest 21-day quarantine for close contacts** of confirmed or suspected mpox cases in closed communities:

- Jails, military barracks, orphanages, dormitories, nursing homes, homeless shelters, evacuation centers, and other similar settings

Certainty of evidence: None
Strength of recommendation: N/A

* *This Good Practice Statement is based on expert consensus intended to support best practice but is not a mandatory recommendation.*
** *WHO definition of close contact (Aug 26, 2024)*[165]

Guideline Panel Considerations

The panel acknowledged that the overall certainty of evidence regarding the effectiveness of quarantine for mpox close contacts is very low, primarily due to methodological limitations in observational studies and the indirect nature of evidence derived from mathematical models.

The GP adopted the WHO definition of close contact for mpox, which includes: (1) skin-to-skin (including sexual contact) and mouth-to-mouth or mouth-to-skin contact, and (2) being face-to-face with someone who has mpox (which can generate infectious respiratory particles).[165]

The panel also adopted the WHO definition of high-risk individuals for mpox, which include: (1) health and care workers at risk of exposure; (2) people in the same household or close community as someone who has mpox, including children; (3) people who have multiple sex partners, including men who have sex with men; and (4) sex workers of any gender and their clients.[165]

The panel expressed significant concerns that recommending general quarantine for mpox close contacts would be a disproportionate and resource-intensive public health intervention given the disease's low transmission efficacy. They highlighted lack of studies on the benefits and harms of such a widespread quarantine, noting potential negative impacts such as high resource use (e.g., lost wages, extensive healthcare monitoring), and significant psychosocial and economic issues for affected individuals and families.

Also raised were equity concerns, as mandatory quarantine could exacerbate disparities for marginalized groups, including low-income households and incarcerated individuals, and potentially lead to stigma. While acknowledging that targeted quarantine in high-risk settings (like closed institutions or for immunocompromised contacts) might be conditionally feasible and beneficial, the general recommendation for quarantine faces challenges in terms of logistical capacity, community acceptability (as it may be seen as a disproportionate response), and overall resource availability, making active monitoring with prompt isolation of symptomatic contacts a more preferred and feasible alternative.

Despite concerns regarding general quarantine, the panel recognized that specific environments, such as jails, military barracks, dormitories, evacuation centers, and similar closed settings, present unique challenges where physical distancing and infection prevention measures are difficult to maintain. In these high-risk settings, the potential for rapid and widespread mpox transmission is substantially increased.

The panel emphasized the need to protect individuals with immunocompromising conditions, who may be at increased risk for severe mpox. The panel adopted the CDC definition of individuals with immunocompromising conditions and treatments, which include but are not limited to: (1) HIV infection, particularly in the presence of a low CD4 count (<200 cells/mm^3); (2) moderate or severe primary immunodeficiency (e.g., phagocyte disorders, agammaglobulinemia, common variable immunodeficiency disease, severe combined immunodeficiency, DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia telangiectasia, or any other immunodeficiency with immune dysregulation); (3) active treatment for a solid tumor or hematologic malignancy; (4) immunosuppressive therapy for solid-organ or islet transplant; (5) active treatment with high-dose corticosteroids (i.e., 20 or more mg of prednisone or equivalent per day when administered for 2 or more weeks), an alkylating agent, antimetabolite, transplant-related immunosuppressive drug, cancer chemotherapeutic agent classified as severely immunosuppressive, tumor necrosis factor (TNF) blocker, or other biologic agent that is immunosuppressive or immunomodulatory; and (6) receipt of chimeric antigen receptor (CAR)-T-cell therapy or hematopoietic cell transplant (within 2 years of transplantation or taking immunosuppressive therapy).[166] Active monitoring of exposed contacts and advising them to avoid direct interaction with such individuals for 21 days post-exposure was viewed as a pragmatic, low-burden intervention that addresses transmission risks while preserving individual freedoms.

Overall, the GP issued a weak recommendation against mandatory quarantine for close contacts of suspected or confirmed mpox cases in the general community alongside two Good Practice Statements supporting active symptom monitoring and avoiding direct interaction with immunocompromised individuals as well as targeted quarantine for closed community settings. These recommendations reflect a balanced appraisal of available evidence, contextual factors, and ethical considerations.

The recommendations align with current WHO guidance, which does not advocate for universal quarantine of mpox contacts, but emphasizes symptom monitoring, timely identification of secondary cases, and isolation of symptomatic individuals. The targeted approach proposed by the panel reflects global best practices, while incorporating context-specific considerations relevant to the Philippine setting.

Key Findings

- Of the 6 studies which reported the effects of quarantine, 2 observational studies (N = 497) showed that quarantine of 22 and 28 days after being exposed to a confirmed case of mpox resulted in no incidence of mpox, 3 modeling studies support the effectiveness of quarantine in reducing mpox transmission and 1 modeling study found the 21-day mandatory quarantine detected 83% of mpox cases.
- The certainty of evidence is very low since the observational studies demonstrated high risk of confounding bias, while the effect of quarantine on other mpox transmission were based only on modeling studies with some concerns on study quality.

Background

Mpox is a zoonotic disease caused by the monkeypox virus (MPXV), an orthopoxvirus similar to smallpox. It affects all ages and manifests as painful rash, enlarged lymph nodes, headache, fever, muscle ache and back pain.[165] Mpox can be transmitted from person to person mainly through close contact (including skin-to-skin, mouth-to-mouth, mouth-to-skin, or face to face) with someone who is infected with mpox. Other means of transmission include sexual contact, contact with contaminated objects, and perinatal transmission.

Mpox is now considered an emerging infectious disease that has been increasing in number in different parts of the world, including the Philippines. As of April 30, 2025, WHO reported a total of 142,242 laboratory confirmed cases, including 328 deaths worldwide.[167] Among the 47 countries outside Africa, there were 3,979 new confirmed cases and 11 new deaths. In the Philippines, WHO reported a total of 136 confirmed cases and 4 deaths.

Among infectious diseases, quarantine of both the infected individuals and their close contacts is one of the most effective strategies in decreasing the incidence.[168] Quarantine is defined as the physical separation and restriction of movement of individuals exposed to a certain infectious disease. They may or may not be infected or ill but may become infectious to others.[169] Currently, there is no evidence in the Philippines that exists on the recommended quarantine period among individuals who have been exposed to confirmed and suspected mpox patients.

Summary of the Evidence

Characteristics of included studies

Observational studies on quarantine and isolation of exposed individuals

We found 2 observational studies (N = 497) obtained from case investigations of close contacts of confirmed mpox cases. The first was an observational study from England (Ladhani 2022) including 340 school children (age 2 to 16 years) and 100 adult staff members who were exposed to an index case/s of mpox.[170] The exposed children and staff members were excluded from school, quarantined and isolated at home (but without the need for self-isolation) for 21 days. These individuals were also advised to avoid contact with high-risk individuals (e.g., other young children, pregnant women, immunosuppressed individuals). All had medium-risk exposures (i.e., contact within 1 meter with an mpox case for ≥ 15 minutes or sharing a car ride). One subgroup composed of 90 children 4–

5 years old and 10 staff members in the reception year (1st year of primary school) were allowed to remain in school but in separate bubbles from other unexposed children. Among 186 children aged 2–11 yrs who were offered a vaccine, 21 (11%) received one dose of MVA-BN 1–2 weeks after exposure. Follow-up testing was done after 28 days to confirm positive cases.

The second study (Hagan 2022) was a case investigation of 57 male residents (median age: 38 years) in a county jail in Chicago, Illinois, United States between July to August 2022 who were exposed to an mpox case within 7 days from symptom onset.[171] All residents were reported to have low knowledge regarding mpox symptoms and transmission modes. Residents denied having sexual or intimate contact with the mpox case, and all exposures were classified as intermediate-risk (i.e., within 5 feet for ≥3 hours without mask). All were quarantined in their dormitories for 21 days and were asked to monitor symptoms daily. Post-exposure prophylaxis within 7–14 days of exposure using MVA-BN vaccine (Jynneos) was accepted only by 13/57 (23%) residents. Incidence of mpox was assessed using anti-Orthopoxvirus IgM at day 15 and 22, but only 14 (24.5%) consented to serological testing.

Modeling studies on quarantine and isolation

Four modeling studies using various dynamic models (deterministic, game-theoretical, stochastic, and probabilistic) assessed the impact of quarantine on mpox transmission. Four studies, one from Tanzania (Leandry 2022),[172] one from Bangladesh (Ullah 2024),[173] and one from the United States[174] focused on exposed close contacts and reported a reduction in new mpox cases with quarantine, though only one study[174] specified a 14-day duration. Another study from China (Deng 2024) assessed the impact of the existing 21-day mandatory quarantine for incoming travelers and optional quarantine on the rate of detected mpox cases.[175]

Efficacy outcomes

Incidence of mpox (2 observational studies, N = 497, very low certainty)

In the two observational studies, no mpox cases were recorded (0%, 95% CI 0–2%, $I^2 = 3.0\%$) at the 22- to 28-day follow-up following medium/intermediate-risk exposure to an mpox case.[170,171] In one study, after a 28-day follow-up, 0 mpox cases were confirmed out of the 440 total exposed individuals in the study.[170]

Mpox transmission (4 modeling studies, very low certainty)

Mathematical modeling studies consistently support the effectiveness of quarantine and vaccination in reducing mpox transmission, though their impact varies by setting, adherence, and resource constraints. Leandry (2023) used a deterministic dynamic model, which employs fixed equations to produce a single, predictable outcome from a given set of parameters, assuming average behavior in a population, to show that quarantine significantly reduces the reproductive number (R_0) of mpox, with greater impact when quarantine rates are higher and vaccination is added.[172] Ullah (2024) also applied a deterministic model incorporating human behavior, showing that 14–28 days of quarantine slowed transmission and led to epidemic fadeout when strictly followed, but high quarantine costs may reduce adherence and increase cases.[173]

Savinkina (2024) used a stochastic model, which incorporate random variation in transmission events, allowing for multiple possible outcomes that reflect real-world uncertainty and variability, on a United States college campus and found that 14-day quarantine of contacts provided little incremental benefit when 50% of cases were detected and isolated, with large numbers needing quarantine per detected case (as many as 200 students).[174] Isolating 20%, 50%, and 80% of cases could avert 33%, 50%, and 85% of secondary transmissions over 100 days, respectively. Quarantine was not shown to reduce likelihood of outbreak but did reduce average number of cases per outbreak when R_0 was 2.4.

Rate of detection of mpox cases (1 modeling study, very low certainty)

Deng (2024) applied a probabilistic model and found China's **21-day mandatory quarantine for incoming travelers detected up to 83% of mpox cases** and was more effective than self-reporting or voluntary isolation, which relied heavily on individual compliance and only detected 46% of cases.[175]

Safety outcomes

No studies were found assessing the adverse effects of implementing quarantine on close contacts of mpox cases.

GRADE summary of findings table

Table 27 shows the efficacy and safety outcomes in quarantine vs. no quarantine for mpox.

Table 27. Quarantine compared to no intervention for mpox.

Outcomes	Basis (№ and type of studies, total participants)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty of Evidence
			No quarantine	Quarantine	Difference	
Efficacy outcomes						
Incidence of mpox Assessed *via*: RT-PCR or Serology (IgM) Follow-up: range 22–28 days	2 non-randomized studies (N = 56)	N/A	10.2%[a]	**0.0%** (0 to 2%)	**10.2 fewer cases per 100** (10.2 fewer to 8.2 fewer)	⊕◯◯◯ Very low[b,c]
Mpox transmission Assessed *via*: Reproductive number (R_0) Follow-up: range 14–28 days	3 modeling studies	Mathematical modeling studies suggest that quarantine—particularly when combined with vaccination—**can reduce mpox transmission, though effectiveness varies by adherence, setting, and resource availability**. Deterministic models showed reduced viral reproductive number and epidemic fadeout with strict quarantine, while stochastic models highlighted limited added benefit of contact quarantine over case isolation.				⊕◯◯◯ Very low[d,e,f,g]
Rate of detection of mpox cases Assessed *via*: RT-PCR Follow-up: range 21 days	1 modeling study	Probabilistic modeling indicated that 21-day mandatory quarantine of international travelers **detected more cases (83%)** than self-reporting / optional quarantine approaches (46%)				⊕◯◯◯ Very low[d,f,g]
Safety outcomes - not reported						

a Zheng 2024 systematic review (https://doi.org/10.1016/j.bj.2024.100823): secondary attack rates (SARs) ranged from 0 to 10.2%, but a median SAR of 50% was reported among 16 households in a recent study.
b Moderate risk bias due to confounding.
c Different outcome measures used to confirm mpox positivity. Population in Ladhani 2022 involved mostly children in the UK, while Hagan 2022 involved male young adults in Chicago, USA.
d Modeling studies demonstrated serious risk of bias. As no validated 'Risk of bias' checklist for mathematical transmission models was available, we assessed whether the modelling and reporting followed the best practice recommendations of the International Society for Pharmacoeconomics and Outcomes (ISPOR) and the Society for Medical Decision making (SMDM) for dynamic mathematical transmission models. Majority of the studies included moderate to major concerns.
e Impact of quarantine shown to differ depending on setting, adherence, resource constraints, and if vaccination was provided.
f Evidence is based on modeling studies.
g The outcome in the modeling studies included did not present the confidence interval of the results.

Certainty of the Evidence

Overall certainty of evidence was downgraded to **very low** due to very serious risk of bias and imprecision across critical outcomes.

Of the seven studies on quarantine, two observational studies had a serious overall risk of bias due to confounding (i.e., exposures were limited to category 2 (medium risk)), co-intervention (i.e., vaccination was included as part of quarantine intervention), and measurement bias (i.e,. reporting of skin-to-skin or sexual contact might not have been reliable; several missing data). Sharing utensils, linens also could not be reliably assessed). The four modeling studies had a very serious risk of bias due to study design limitations and very serious imprecision from the absence of confidence intervals in the outcomes. These modeling studies were appraised based on reporting quality; three of the five had moderate to major concerns due to non-dynamic models, unclear uncertainty analyses, and unclear reporting of estimated changes in infection burden.

Other Considerations

Resource implications (cost/cost-effectiveness)

One systematic literature review by Alsharani *et al.* investigated the expected economic cost for healthcare systems of quarantine in the case of mpox virus outbreaks. Indirect evidence was taken from economic studies on COVID-19 and SARS in China.[176] In the case of mpox, quarantine strategies effectively reduce the infection rate and delay new infections over time, but the healthcare departments would have to incur huge expenses particularly from the indirect costs of quarantine. The availability of effective treatments and vaccines suggests that the high costs associated with quarantining infected individuals and close contacts would be difficult to justify. Implementing widespread quarantine for close contacts of confirmed mpox cases could significantly impact national gross domestic products and lead to substantial productivity losses.

Stakeholder values, preferences, and acceptability

Rapid review done by the United Kingdom Health Security Agency found no evidence on values and preferences regarding quarantine.[177] One local study was done where senior citizens showed positive attitudes towards the implementation of the enhanced community quarantine during COVID-19, specifically on self-isolation and following barangay rules and regulations.[178] Likewise, among adolescents in the Philippines, a local study showed that adolescents perceive isolation in three primary ways: as a constraint, a necessity and an opportunity.[179]

Equity and feasibility

The duration of quarantine would probably be patterned after the known incubation period and duration of infectivity of the mpox virus, as well as other considerations by policymakers (e.g., resources available, indirect costs due to missed workdays). Across 8 studies, the mean incubation period for mpox ranged from 7.1 to 9.1 days, with 5^{th}–95^{th} percentiles spanning approximately 2 to 23 days.[180-187] Several studies reported pre-symptomatic viral DNA detection 1–4 days before symptom onset.[181] Generation time and serial interval estimates (i.e., days between the date of infection of a confirmed case and those of secondary cases) ranged from 8.0 to 12.5 days.[180-185] **Findings support quarantine durations of up to 21 days to account for longer incubation in a minority (~5%) of cases.**

Viral loads were significantly higher in skin and anal samples than in throat or nasopharyngeal samples (median cycle threshold (Ct) 22.0 vs 29.0 and 36.5; $p = 0.0013$).[187] MPXV DNA was most frequently detected in skin lesions (94.4%) and showed the longest median time to viral clearance (16 days).

Guideline Question 10.
Mpox Vaccination for High-Risk Individuals

Should mpox vaccine be given to persons at risk?

Recommendation 10.
We suggest the use of mpox vaccines as pre-exposure and post-exposure prophylaxis for persons at risk*.

Certainty of evidence:	Very Low
Strength of recommendation:	Weak

**WHO definition of high risk individuals*[165]

Guideline Panel Considerations

Despite very low certainty of evidence, the GP issued a weak recommendation supporting mpox vaccination for at-risk individuals, considering both public health benefit and contextual realities. The panel adopted the WHO definition of high-risk groups, which include: (1) health care workers at risk of exposure; (2) people in the same household or close community as someone who has mpox, including children; (3) people who have multiple sex partners, including men who have sex with men; and (4) sex workers of any gender and their clients.[165] Evidence suggests vaccination offers modest protection against infection and disease severity, with an acceptable safety profile.

However, feasibility and equity concerns were emphasized. The MVA-BN vaccine remains unavailable in the Philippines, requires cold chain logistics, and is prohibitively expensive at approximately US$ 65 per dose (₱3,640) which limits access especially for vulnerable populations. The panel stressed that while vaccination for at-risk individuals is crucial for public health, its feasibility is compromised without government subsidy and expedited FDA registration, hindering equitable access and widespread implementation. Given these factors, vaccination remains a critical but currently constrained tool for mpox prevention among at-risk groups.

Key Findings

- Nineteen studies (N = 53,843) investigated the effect of vaccines on at-risk patients in preventing mpox infection.
- Based on eight studies, the incidence of mpox was lower in patients who received mpox vaccines as compared to patients who have not received mpox vaccine. For patients receiving the vaccine as a pre-exposure prophylaxis, there is no statistical difference on the risk of developing mpox as compared to those not given the vaccine. Alternatively, patients who took the mpox vaccine as a post-exposure prophylaxis had lesser risk of developing mpox.
- Eight studies experimented on the VE of the mpox vaccines. Based on the pooled results, there is a beneficial effect of giving vaccines to at-risk patients in preventing mpox.
- One study analyzed the severity of mpox among patients who were given the vaccine as compared to those with no vaccine. The outcome of this study showed that there is a lower risk of developing severe mpox in vaccinated patients
- One study showed that a single dose of vaccine for post-exposure prophylaxis provided antibody and cellular immune response in children which may last up to 15 weeks.

- Two studies showed adverse effects that may be experienced by patients receiving the vaccine, however this may only be minimal and mild.

Background

In 2022, an outbreak of mpox has been reported in at least 30 countries.[188] As specific treatment for mpox is still lacking, the rising outbreak has raised efforts into studies on potential treatment and prevention. High-risk groups that may potentially develop mpox or may progress to severe disease include children, pregnant women, and immunocompromised individuals, including men having sex with men (MSM), and people with human immunodeficiency virus (HIV) infection.[189]

Mpox vaccines have been tested in different studies in terms of providing protection from mortality, reducing severity of clinical symptoms and reducing viral loads and increasing antibodies against mpox.[190] There are currently three types of vaccines that may be used for the prevention of mpox. The first vaccine is ACAM2000, a replicating vaccinia virus-based second-generation smallpox vaccine. The vaccine is administered as a single dose *via* the percutaneous route. The second vaccine is the Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN), popularly known as Jynneos, Imvamune in the European Union, and Imvanex in Canada. It is a replication-deficient live virus vaccine enclosed in a non-replicating Orthopoxvirus-MVA-BN virus. It is administered in two doses of 0.5 mL subcutaneously, 4 weeks apart. The third vaccine is the LC-16 (KM Biologics, Japan), a third-generation smallpox vaccine. It is an attenuated partially replicating Lister strain of vaccinia. It is administered *via* the subcutaneous route as a single dose.[191]

The rationale of this evidence review is to determine the efficacy and safety of mpox vaccines among at-risk patients in preventing and decreasing severity of mpox.

Summary of the Evidence

Characteristics of included studies

We found 19 studies that included a total of 53,843 patients.[192-210] The pooled studies include a mix of study designs: 10 observational studies, 5 cohort studies, 3 case-control studies, and 1 RCT.[208] Nine studies were performed in the United States of America, two studies performed in Spain, two studies performed in France, two studies performed in Canada and single studies were performed individually in the United Kingdom, Israel, Japan, and the Netherlands. The studies involved adults at high risk of mpox infection, including MSM, individuals with HIV or sexually transmitted infections, high-risk contacts, and in one case, children.[200]

Eighteen studies used the MVA-BN vaccine, and one study (Tomita 2023) assessed the live attenuated smallpox vaccine LC-16.[204] Eight studies investigated on the effect of mpox vaccine as pre-exposure prophylaxis whereas eleven studies explored the effects of mpox vaccine as post-exposure prophylaxis. The primary intervention across studies was the MVA-BN vaccine, administered either as 1 dose or 2 doses given 4 weeks apart, used for pre-exposure or post-exposure prophylaxis.[192-194,196]

Outcomes assessed focused mainly on VE or efficacy, typically measured by incidence or onset of mpox, or breakthrough infection.[201,202,207] Some studies also reported immunogenicity and adverse effects.[200,204] Follow-up durations varied from as short as 21 days[198] to as long as 12 months,[202] with outcomes ascertained through clinical or laboratory-confirmed diagnosis of mpox.

Efficacy outcomes

Incidence of Mpox

Based on 8 observational studies that assessed MVA-BN mpox vaccines, the vaccine may reduce mpox incidence (1,503/12,280 or **12.3%** in vaccinated vs. 14,005/19,014 or **73.7%** in unvaccinated groups) with a corresponding OR

0.24 (95% CI 0.06–1.02). The evidence is very uncertain due to the non-randomized design of the included studies, inconsistency/high statistical heterogeneity, and imprecision in the estimates (upper CI crossing 1.00).

When given as **pre-exposure prophylaxis,** MVA-BN vaccine may reduce the risk of developing mpox (11.5% with vaccination vs. 63.2% without; OR 0.38, 95% CI 0.12–1.23), but results were likewise very uncertain. Effect estimates for benefit were more precise in studies that used mpox vaccine as a **post-exposure prophylaxis**, with 12.4% developing mpox versus 82.7% in unvaccinated groups (OR 0.14, 95% CI 0.03–0.79)

Vaccine effectiveness

Based on eight observational studies, vaccination against mpox was associated with a 51% reduction in the odds of developing mpox compared to no vaccination (OR 2.04, 95% CI 1.80–2.32), corresponding to a **VE of 51% (95% CI 44–57%).**

Subgroup analysis showed that when administered as pre-exposure prophylaxis, the vaccine was associated with a **VE of 52% (95% CI 44–59%)** (OR 2.06, 95% CI 1.77–2.41). When used as post-exposure prophylaxis, the vaccine was associated with a **VE of 50% (95% CI 37–60%)** (OR 1.98, 95% CI 1.59–2.47).

While these findings suggest a protective effect of mpox vaccination in both pre- and post-exposure situations, the certainty of evidence should be assessed considering potential limitations in the observational study designs, including risk of bias, indirectness, and imprecision.

Severity of mpox

One retrospective study from France analyzed the severity of mpox among patients who were given the vaccine as post-exposure prophylaxis as compared to those with no vaccine.[193] Eleven out of 108 patients **(10.2%)** given the vaccine and 97 out of 108 patients **(89.8%)** without vaccination experienced severe symptoms of mpox. Post-exposure mpox vaccination may result in less risk of severe mpox (OR 0.01, 95% CI 0.01–0.03).

Immune response/immunogenicity

One observational study (post-vaccine implementation surveillance) in the United Kingdom assessed the immunogenicity of a single dose of MVA–BN (0.5 mL containing $0.50–3.95\times10^8$ infectious units of MVA-BN live virus) in children.[200] Antibody levels were measured using a test that reports absorbance (optical density at 450 nm; OD_{450}) values—higher values mean more antibodies. The vaccine induced robust humoral and cellular immune responses up to 15 weeks post-vaccination. IgG measurement showed mean absorbances of 1.380 (well above cutoff for strong antibody response of OD_{450} >0.1926) at 6 weeks and 0.9826 at 15 weeks post-vaccination. All vaccinated children developed high levels of poxvirus-specific IgG antibodies and activated T-cell responses, including memory and cytotoxic subsets. However, the certainty of evidence for this outcome is very low due to the small sample size, lack of a control group, and imprecision in estimates.

Safety outcomes

Any adverse events: MVA-BN

In children, 2 studies showed adverse effects that may be experienced by the patients receiving the vaccine. No symptoms were reported by 16 (36%) of 45 children, whereas 18 (40%) reported local reaction only (mainly swelling [20 (44%)] and pain [18 (40%)] at injection site and 11(24%) reported systemic symptoms (mainly rash [5 (11%)] and fever or feeling hot [5 (11%)]) with or without local reactions.

Other studies from vaccine safety monitoring databases found that MVA-BN (Jynneos) appears well tolerated. In a Korean study (n = 142), common local reactions after the first dose included **pruritus (66.2%), redness (48.1%), and swelling (49.4%)**, with similar or slightly higher rates after the second dose; **fatigue was the most frequent systemic symptom** (37.7% after dose 1, 24.6% after dose 2). In the United States, among over 1.2 million Jynneos doses administered, the **reported myocarditis rates were 2.69 and 8.64 per million doses** after the first and second doses, respectively, with **no unexpected safety concerns** identified in national surveillance systems.

Any adverse events: LC-16

In adults, adverse events due to inoculation, such as rash (83%), fever (33.3%), lymphadenopathy (33.3%), and local reaction at the inoculation site (comprising erythema, swelling, induration, and pain) (16.7%) were observed in the participants; however, all inoculation-related events were non-severe and non-serious, and the participants recovered during the 28-day observation period.

GRADE summary of findings table

Table 28 shows the efficacy and safety outcomes in mpox vaccine vs. no intervention for high-risk patients.

Table 28. Mpox vaccine compared to no intervention for high-risk patients.

Outcomes	Basis (№ and type of studies, total participants)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty of Evidence
			No mpox vaccine	Mpox vaccine	Difference	
Efficacy outcomes						
Incidence of Mpox	8 non-randomized studies (N = 31,294)	**OR 0.24** (0.06–1.02)	73.7%	**40.2%** (14.4–74)[j]	**33.5% fewer** (59.3 fewer to 0.4 more)	⊕◯◯◯ Very low[a,b,c]
Incidence of Mpox with pre-exposure prophylaxis	4 non-randomized studies (N = 10,994)	**OR 0.38** (0.12–1.23)	63.2%	**39.5%** (17.1–67.8)	**23.7% fewer** (46.1 fewer to 4.7 more)	⊕◯◯◯ Very low[a,c,d]
Incidence of Mpox with post-exposure prophylaxis	4 non-randomized studies (N = 20,300)	**OR 0.14** (0.03–0.79)	82.7%	**40.1%** (12.5–79.1)	**42.6% fewer** (70.2 fewer to 3.6 fewer)	⊕◯◯◯ Very low[a,e]
Severity of Mpox	1 non-randomized study (N = 216)	**OR 0.0129** (0.0053–0.0311)	89.8%	**10.2%** (4.5–21.5)	**79.6% fewer** (85.3 fewer to 68.3 fewer)	⊕⊕◯◯ Low[a]
Immunogenicity	1 non-randomized study	IgG antibodies showed mean absorbances of 1.380 (well above cutoff for strong antibody response of OD_{450} >0.1926) at 6 weeks and 0.9826 at 15 weeks post-vaccination.				⊕⊕◯◯ Low[a]
Vaccine effectiveness (VE)	8 non-randomized studies	**OR 2.04** (1.80–2.32) **VE 51%** (44–57%)				⊕⊕◯◯ Low[a]
VE with pre-exposure prophylaxis	4 non-randomized studies	**OR 2.06** (1.77–2.41) **VE 52%** (44–59%)				⊕⊕◯◯ Low[a]
VE with post-exposure prophylaxis	4 non-randomized studies	**OR 1.98** (1.59 –2.47) **VE 50%** (37–60%)				⊕◯◯◯ Very low[a,f]

Outcomes	Basis (№ and type of studies, total participants)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty of Evidence
			No mpox vaccine	Mpox vaccine	Difference	
Safety outcomes						
Adverse effects	2 non-randomized studies	No symptoms were reported by 16 (36%) of 45 children, whereas 18 (40%) reported local reaction only (mainly swelling [20 (44%)] and pain [18 (40%)] at injection site) and11(24%) reported systemic symptoms (mainly rash [five (11%)] and fever or feeling hot [five (11%)]) with or without local reactions. In adults, adverse events due to inoculation, such as rash, fever, lymphadenopathy, and local reaction at the inoculation site (comprising erythema, swelling, induration, and pain) were observed in the participants; however, all inoculation-related events were non-severe and non- serious, and the participants recovered during the 28-day observation period				⨁⨁◯◯ Low[a]

a High risk of bias due to confounding
b I^2 = 99%
c CI for OR crossed 1.00
d I^2 = 94%
e I^2 = 95%
f I^2 = 72%

Certainty of the Evidence

Overall certainty of evidence was downgraded to **very low**.

Out of the 19 studies, 18 had an overall high risk of bias due to lack of blinding and other confounders that may affect the result of the outcomes. Since most of the studies are case-control and observational studies, there are risks of selection and attrition bias. Evidence was further downgraded due to imprecision (CI crossing 1.00 in some outcomes) and inconsistency (high statistical heterogeneity).

Other Considerations

Cost of vaccination

Mpox vaccine (MVA-BN, Jynneos) currently costs around US$65 (₱3,640) per dose.

Cost-effectiveness

No local cost-effectiveness studies were identified.

A United Kingdom study determined the cost-effective vaccination strategy for reducing outbreaks of mpox among gay, bisexual and other men who have sex with men (GBMSM). All vaccination strategies were cost-saving compared to no vaccination.[211] Based on their analysis, the average total cost per mpox case was £2,772 (₱207,900), driven by productivity losses (£1,601 or ₱120,075), followed by case-management (£755 or ₱56,625) and public health costs (£416 or ₱31,200).

Stakeholder values, preferences, and acceptability

No local research evidence was identified. Other related studies showed that mpox vaccine acceptance varies widely across populations, with higher uptake among MSM and LGBTI communities (up to 90%) and lower rates among the general public and healthcare workers (as low as 43–55%), influenced by factors such as perceived risk, prior vaccination, HIV status, and access to information and services.

A systematic review of 11 studies including 8,045 participants estimated a pooled mpox vaccine acceptance rate of 56% (95% CI 42–70%) and vaccine hesitancy rate of 24% (95% CI 8–40%). Acceptance rates were lower in Asian countries (50%) compared to Europe (70%), potentially reflecting differences in disease incidence and perceived risk.[212] Subgroup analyses revealed variability across populations: vaccine acceptance was lowest among the general public (43%, 95% CI 35–50%) and healthcare workers (63%, 95% CI 42–70%), and highest among the LGBTI community (84%, 95% CI 83–86%).

A 2022 cross-sectional study showed a high acceptance rate of 90.2% among MSM in China.[213] Key factors associated with vaccine acceptance included awareness of mpox and preventive measures, perceived susceptibility to infection, and potential exposure through travel or contact with individuals or animals from endemic regions. In participants with self-reported HIV infection, additional factors such as education level and inconsistent condom use were also influential. In a 2023 survey of 1,656 mpox vaccine priority individuals (GBMSM) in Taiwan, 43% were unvaccinated, 13% had one dose, and 44% completed two doses.[214] Full vaccination was linked to HIV status, multiple sexual partners, HIV pre-exposure prophylaxis use, and prior HPV vaccination. Despite free vaccine availability, uptake and completion remain suboptimal, highlighting the need for greater awareness and access in high-risk groups.

Another survey, conducted between June and August 2022 among healthcare workers in France and Belgium (n = 397; mean age 43.3 years; 65% female), reported a low vaccine acceptance rate of 55.4%.[215] The researchers attributed this to factors such as complacency, pandemic fatigue, trust in public health guidance, and perceived exposure risk. Notably, only 31% of respondents said they would get vaccinated as soon as possible, while 25% indicated probable intent and 22% remained undecided. Acceptance increased to 79% if mpox spread to the general population, with higher uptake among physicians and pharmacists (84.7%) compared to nurses (70.7%).

Equity and feasibility

Mpox vaccine is currently not available in the Philippines. Jynneos, once thawed or refrigerated, is good for either 4 or 8 weeks, allowing some time to schedule a second dose. The vaccine at frozen storage can last about 18 months.

Guideline Question 11.
Mpox Treatments

Should antiviral medications and immunoglobulins be given to patients with confirmed mpox infection?

Recommendation 11.1.
We recommend against the use of tecovirimat for patients with confirmed mpox infection.

Certainty of evidence:	High
Strength of recommendation:	Strong

Recommendation 11.2.
We suggest the use of topical cidofovir for patients with confirmed mpox infection.

Certainty of evidence:	Very Low
Strength of recommendation:	Weak

Recommendation 11.3.
We recommend against the use of brincidofovir or vaccinia immunoglobulins for patients with confirmed mpox infection.

Certainty of evidence:	Very Low (no evidence)
Strength of recommendation:	Strong

Guideline Panel Considerations

The GP initially made a weak recommendation against the routine use of tecovirimat for confirmed mpox infection due to the absence of high-quality evidence demonstrating clinical benefit, as well as concerns regarding accessibility and cost. Although tecovirimat is considered a promising antiviral, its use remains off-label for mpox in the Philippines, and no improvement in key clinical outcomes was observed in available studies.

Following the publication of the PALM007 randomized controlled trial, the initial recommendation was updated through a Delphi process where a consensus was reached to upgrade the initial recommendation to a *strong* recommendation against the use of tecovirimat for patients with mpox. This decision was primarily driven by the high-certainty evidence from the new RCT, which addressed key limitations of earlier studies, such as small sample sizes and bias, and which demonstrated no significant clinical benefit of tecovirimat across critical outcomes. The findings were consistent with prior non-randomized studies, further reinforcing the conclusion. Panelists also noted that tecovirimat has non-trivial adverse effects (e.g., headache, nausea), and with no demonstrated benefit, the risk-benefit balance does not favor its use. In addition, access and equity concerns remain significant, particularly in settings like the Philippines where tecovirimat is still unregistered and faces cost and logistical barriers. A strong recommendation helps guide equitable resource allocation and still allows for clinical discretion in exceptional cases.

For topical cidofovir, while preliminary data suggest potential benefit in accelerating lesion resolution, limitations in the evidence, small sample size, and frequent local adverse effects led the panel to only suggest its use.

The panel issued a strong recommendation against the use of brincidofovir or vaccinia immunoglobulins due to the complete lack of evidence for their efficacy or safety in mpox treatment.

Additional factors influencing the panel's recommendations included significant logistical barriers. A major concern raised was that these drugs are currently unregistered in the Philippines, necessitating costly procurement processes that create substantial obstacles to widespread availability. This limited accessibility, coupled with the absence of cost-effectiveness data, raises serious equity concerns, as it could exacerbate disparities and disadvantage patients in low-resource settings.

The GP expressed significant reservations regarding the routine use of antiviral medications and immunoglobulins for confirmed mpox infection, primarily due to the lack of clear evidence demonstrating their clinical benefit.

Key Findings

- Initial recommendations were based on two non-randomized studies (N = 156) investigated the effect of tecovirimat, and one non-randomized study (N = 24) investigated the effect of cidofovir compared to standard of care as treatment for patients with mpox. A recently published placebo-controlled RCT (PALM007) on tecovirimat involving 597 patients was also added to the evidence base.
- Tecovirimat did not show significant effect in terms of reducing time to symptom resolution, time to subjective symptom improvement, or MPXV PCR Ct. Data from the PALM007 RCT also did not show any significant advantage in terms of time to lesion resolution, decline in the proportion of patients with positive PCR results, and safety.
- Cidofovir, used topically, was found to be associated with significant decrease in time to skin lesion resolution. Mild systemic adverse effects were reported for tecovirimat, while mild to moderate skin irritation was reported for topical cidofovir.
- No studies were found involving brincidofovir and vaccinia immunoglobulin.

Background

Because of the global scale and the emerging nature of mpox, several treatment options have been suggested against this disease, including the antivirals tecovirimat, brincidofovir and cidofovir, and the vaccinia immunoglobulin. Tecovirimat targets the p37 protein, a viral envelope component essential for orthopoxvirus replication. Cidofovir and its prodrug brincidofovir inhibit viral DNA polymerase activity and thus inhibit DNA replication. Vaccinia immunoglobulin is an antibody preparation targeting the vaccinia virus, which is closely related to the MPXV, and may provide activity against the latter.[216]

Tecovirimat and brincidofovir have been issued emergency use authorizations by the United States FDA for the treatment of mpox,[216] while vaccinia immunoglobulin is available for the treatment of mpox *via* the expanded access protocol of the United States CDC.[216]

This review investigated the effect of tecovirimat, brincidofovir, cidofovir, and vaccinia immunoglobulin compared to placebo or standard of care treatment in influencing clinical outcomes of patients with confirmed mpox.

Summary of the Evidence

Characteristics of included studies

Three studies were obtained following the database search, with two involving tecovirimat[217,218] and one involving cidofovir.[219] Of the 2 studies on tecovirimat, one was a single-center prospective cohort (Mazzotta 2023) involving

oral tecovirimat with a dose of 600 mg for 14 days,[217] while the other was a cross-sectional study (Karmarkar 2024) of patients residing within a geographical area, with no restrictions on tecovirimat route or dose.[218] The total sample size of the tecovirimat studies was 156 (range 41–115), with 99 in the treatment group and 57 in the control group (no tecovirimat). Both studies listed time to symptom resolution, defined respectively as clinician-assessed healing of skin and mucosal lesions by day 21[217] and patient-reported healing of all skin lesions and no subjective symptoms[218] as a primary outcome. Secondary outcomes included change in MPXV PCR Ct values in upper respiratory tract samples after the start of treatment[217] and time to improvement of symptoms, defined as a subjective decrease in pain due to lesions, "feeling better," or any other indication of improving health.[218] Adverse effects were also assessed through patient reports in one study.[218]

Results of a double-blind, randomized, placebo-controlled trial (PALM007) done in the Democratic Republic of Congo have also been recently published (April 17, 2025).[220] In this trial, 597 patients with at least one mpox skin lesion who tested positive for MPXV by PCR were randomly assigned to receive either oral tecovirimat (14 days, dose based on body weight) or placebo in a 1:1 allocation ratio. Patients were stratified according to number of days since symptom onset (≤7 days vs > 7 days) and trial site. Resolution of mpox lesions (i.e., number of days from randomization to first day on which all skin lesions were scabbed) was the primary end point. Other outcomes included adverse events, death, negativity for MPXV at 14 days, and pregnancy outcomes. Follow-up assessments were done at 28 days and 58 days from randomization.

The study involving cidofovir was a single-center prospective cohort study (Sobral-Costas 2023) with 24 patients (12 in each group) and involving topical 1% cidofovir applied on skin lesions twice a day for 14 days.[219] The primary outcome was median number of days until resolution of skin lesions, while the secondary outcome was virological status, assessed through Orthopoxvirus PCR test results after 7 and 14 days in both skin lesion samples and pharyngeal samples. The number and proportion of patients reporting local adverse effects were assessed and rated as mild (irritation, erythema), moderate (skin lesion with moderate pain), or severe (ulceration, severe pain).

No studies were found exploring the effect of brincidofovir or vaccinia immunoglobulin on patient outcomes.

Efficacy outcomes: Tecovirimat

Time to symptom resolution (2 non-randomized studies and 1 RCT, N = 753, high certainty)

Based on 2 non-randomized studies, tecovirimat did not show a significant difference compared to placebo or standard care in reducing the time to symptom resolution. Mazzotta (2023) reported a mean difference (MD) of 3.3 fewer days (95% CI 8.8 fewer to 0.4 more), while the Karmarkar (2024) reported a MD of 1 fewer day (p = 0.56) in patients with severe disease and 6 more days (p = 0.19) in patients with non-severe disease.

In the PALM007 trial, the median days to resolution of symptoms was 7 days with tecovirimat compared to 8 days in placebo. Hazard ratio for days to lesion resolution was 1.13 (95% CI 0.97–1.31, p = 0.14), indicating no significant benefit with tecovirimat. Similar findings were obtained for patients with symptom onset within 7 days before randomization (HR 1.16, 95% CI 0.98–1.37) and >7 days after (HR 1.00, 95% CI 0.71–1.40). At the 28 day follow-up, 288/295 (97.6%) of patients in the tecovirimat group had lesion resolution, compared to 295/302 (97.7%) in the control group.

Time to symptom improvement (1 non-randomized study, N = 115, very low certainty)

One non-randomized study[218] reported that tecovirimat did not show a significant difference compared to standard of care or placebo in reducing the time to subjective symptom improvement in patients with severe disease (MD 4.5 fewer days, p = 0.28) or with non-severe disease (MD 0.5 more days, p = 0.32).

Viral load (1 non-randomized study, N = 24, very low certainty)

One non-randomized study[217] reported that tecovirimat did not show a significant difference compared to standard of care or placebo in lowering the MPXV PCR Ct value over time (log 2 scale average treatment effect -0.03 units, 95% CI -0.58–0.53).

The number of patients testing negative for MPXV at 14 days was evaluated by the PALM007 RCT using RT-PCR of different specimens. RT-PCR cycle-threshold values less than 40 were considered positive. Results showed no significant difference between treatment groups regardless of the specimen type. On lesion specimens, 91.4% (256/280) of patients in the tecovirimat arm tested negative compared to 89.0% (259/291) in the placebo group (RR 1.03, 95% CI 0.97–1.08).

Using blood samples, 140/160 (87.5%) patients in the tecovirimat group versus 141/162 (87%) in the placebo group tested negative for the virus (RR 1.01, 95% CI 0.92–1.09). On oropharyngeal swab specimens, the rate was 55.4% (144/260) versus 52.5% (136/259) in placebo (RR 1.05, 95% CI 0.90–1.24).

Safety outcomes: Tecovirimat

Adverse effects (1 non-randomized study, N = 115, very low certainty)

One non-randomized study[218] reported adverse effects for tecovirimat, with 31.3% (N = 25) of patients experiencing any adverse effect on treatment. The most common adverse effects were headache (12.5%) and nausea (11.3%); other adverse effects included nausea (7.5%), abdominal pain (7.5%), "mental fog" (7.5%), dizziness (7.5%), and diarrhea (6.3%). No moderate or severe adverse effects were reported.

Serious and non-serious adverse effects (1 RCT, N = 597)

A total of 17 serious adverse effects (i.e., Grade 3–5) occurred among 15/295 (5.1%) in the tecovirimat group, while 15 serious adverse effects occurred in 15/302 (5.0%) in the placebo group (RR 1.02, 95% CI 0.51–2.06). Similar rates of non-serious adverse effects were noted at 72.9% and 70.5% (RR 1.03, 95% CI 0.93–1.14) in the experimental and control groups, respectively. Examples of serious adverse effects included infections (e.g., complicated malaria, septic shock, peritonitis), pregnancy/puerperium/perinatal conditions (e.g., fetal death, spontaneous abortion), anemia, respiratory distress. PALM007 trial investigators did not report whether serious adverse effects were related to tecovirimat.

Efficacy outcomes: Cidofovir

Time to symptom resolution (1 non-randomized study, N = 24, very low certainty)

One non-randomized study[219] reported that topical cidofovir is associated with significantly fewer days to lesion resolution (MD 6 fewer days, $p = 0.006$). A corresponding hazard ratio (HR) of 4.572 (95% CI 1.55–13.47) was reported, interpreted as a higher probability of skin lesions resolving in a given period with cidofovir.

Virological status (1 non-randomized study, N = 24, very low certainty)

One non-randomized study[219] reported that topical cidofovir is associated with a significant increase in the proportion of patients with negative Orthopoxvirus PCR results for pharyngeal samples on treatment day 7 (OR 15.00, 95% CI 1.21–185.20). However, no significant difference was reported for skin lesion samples on treatment day 7 (OR 5.71, 95% CI 0.52–62.66) and day 14 (OR 1.00, 95% CI 0.19–5.36), as well as for pharyngeal samples on day 14 (OR not estimable as all samples were PCR negative).

Safety outcomes: Cidofovir

Adverse effects (1 non-randomized study, N = 24, very low certainty)

One non-randomized study[219] reported adverse effects for cidofovir, with 50.0% (N = 6) of patients experiencing irritation or erosions on the topical application site; most patients reported moderate severity (41.7%), while the remainder reported mild severity (8.3%). In 5/12, local adverse effects occurred during the last 2 days of treatment, managed locally with borax poultice. One patient could not tolerate adverse effects and discontinued treatment after 2 applications. No systemic or severe adverse effects were reported.

Efficacy and safety outcomes: Brincidofovir

No research evidence was identified for the effectiveness and safety of brincidofovir as treatment for patients with confirmed mpox infection.

Efficacy and safety outcomes: Vaccinia immunoglobulin

No research evidence was identified for the effectiveness and safety of vaccinia immunoglobulin as treatment for patients with confirmed mpox infection.

GRADE summary of findings table

Table 29 shows the efficacy and safety outcomes of tecovirimat and topical cidofovir vs. no intervention for patients with confirmed mpox infection.

Table 29. Tecovirimat and cidofovir compared to no intervention for patients with confirmed mpox infection.

Outcomes	Basis (№ and type of studies, total participants)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty of Evidence
			No intervention	Intervention	Difference	
Tecovirimat						
Time to recovery/ symptom resolution Assessed *via*: complete healing of lesions and resolution of all symptoms	2 non-randomized studies (N = 156)	*Non-severe disease:* **Median 6.0 days** (*p* = 0.19)	**17 days** (13.2–26.2)	**23 days** (16.0–28.0)	**6 days longer**	⊕◯◯◯ Very low[a]
		Severe disease: **Median -1.0 days** (*p* = 0.56)	**21 days** (17.5–30.5)	**20 days** (14.0–27.5)	**1 day shorter**	⊕◯◯◯ Very low[a]
	1 RCT (N = 597)	**HR 1.13** (0.97–1.31)	**7 days** (7–8)	**8 days** (7–9)	**1 day shorter**	⊕⊕⊕⊕ High
Time to symptom improvement Assessed *via*: patient subjective report	1 non-randomized study (N = 115)	*Mixed severity:* **MD -3.3 days** (-8.8–0.4)	**11.7 days** (7.6–12.7)	**8.4 days** (1.9–9.2)	**3.3 days shorter** (8.8 days shorter to 0.4 days longer)	⊕◯◯◯ Very low[a]
		Non-severe disease: **Median 0.5 days** (*p* = 0.32)	**8.5 days** (5.3–11.8)	**9 days** (7.0–15.0)	**0.5 days longer**	⊕◯◯◯ Very low[a]
		Severe disease: **Median -4.5 days** (*p* = 0.28)	**15 days** (10–17.8)	**10.5 days** (7.0–16.0)	**4.5 days shorter**	⊕◯◯◯ Very low[a]
Viral load Assessed *via*: change in PCR cycle threshold[b]	1 non-randomized study (N = 41)	**MD -0.03 cycles** (-0.58–0.53)	**0.41 Ct cycles** (-0.01–0.84)	**0.38 Ct cycles** (0.13–0.64)	**0.03 Ct cycles lower** (0.58 lower to 0.53 higher)	⊕◯◯◯ Very low[a]
Patients negative for MPXV	1 RCT (N = 571)	**RR 1.03** (0.97–1.08)	**91.4%** (87.6–94.2%)	**89.0%** (84.9–92.1%)	**27 more per 1,000** (from 27 fewer to 71 more)	⊕⊕⊕⊕ High

Outcomes	Basis (№ and type of studies, total participants)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty of Evidence
			No intervention	Intervention	Difference	
Assessed using PCR assay on a skin swab specimen at 14 days						
All-cause mortality Assessed within 58 days	1 RCT (N = 597)	**RR 1.02** (0.30–3.50)	**1.7%** (0.7–3.9%)	**1.7%** (0.7–3.8%)	**0 more per 1,000** (from 12 fewer to 43 more)	⊕⊕⊕◯ Moderate
Adverse effects Assessed *via*: subjective patient report	1 non-randomized study (N = 115)	**31.3% (N = 25)** of patients experienced any adverse effect. No serious adverse effects.[c]				⊕◯◯◯ Very low
Adverse effects Assessed *via*: subjective patient report and vetted by a pharmaco-vigilance committee (up to 58 days)	1 RCT (N = 597)	*Serious adverse effects:* **RR 1.02** (0.51–2.06)	**5.1%** (15/295)	**5.0%** (15/302)	**1 more per 1,000** (from 24 fewer to 53 more)	⊕⊕⊕⊕ High
		Non-serious adverse effects: **RR 1.03** (0.93–1.14)	**72.9%** (215/295)	**70.5%** (213/302)	**21 more per 1,000** (from 49 fewer to 98 more)	⊕⊕⊕⊕ High
Cidofovir						
Time to symptom resolution Assessed *via*: crusting	1 non-randomized study (N = 24)	**HR 4.572** (1.550–13.470) [symptom resolution][d,e]	**50.0%**	**4.2%** (0–34.2)	**45.8% greater probability for faster symptom resolution** (15.8% to 50% greater)	⊕◯◯◯ Very low[f]
		MD 6.5 days (3.7–9.3)	**18.5 days**	**12 days** (11.5–15.0)	**6.5 days shorter** (3.7 to 9.3 shorter)	⊕◯◯◯ Very low[f]
Local adverse effects Assessed *via*: % of patients with mild/ moderate/ severe adverse effects[g]	1 non-randomized study (N = 24)	**6/12 (50%)** experienced at least 1 adverse effect (all non-severe)[h]				⊕⊕◯◯ Low

a The 95% confidence interval (for Mazzotta 2023) and the *p* value (for Karmarkar 2022) lie within the threshold needed for recommending and not recommending treatment

b Change in PCR Ct measures the change in viral load over time and is not an outcome of interest in this review question. The lower the Ct value (i.e., fewer cycles are needed to obtain a positive test result) implies a greater the amount of viral RNA present in the tested sample.
c The most common adverse effects were headache (12.5%) and nausea (11.3%); other adverse effects included nausea (7.5%), abdominal pain (7.5%), "mental fog," (7.5%) dizziness (7.5%), and diarrhea (6.3%). No moderate or severe adverse effects were reported.
d Interpreted as a higher probability, in favor of the cidofovir-treated group, of skin lesions resolving in a given period.
e Median number of days until lesion resolution was significantly shorter (12 [11.5-15] vs 18 [16- 21]; p = 0.006) in cidofovir. Values converted to mean (SD).
f The sample size does not meet the criteria for optimal information size.
g Mild (irritation, erythema), moderate (skin erosion with moderate pain), severe (ulceration, severe pain).
h 1/6 mild and 5/6 moderate. All 6 reported irritation or erosions on and around the site of application producing local discomfort. In 5/12, local adverse effects occurred during the last 2 days of treatment, managed locally with borax poultice. One patient could not tolerate adverse effects and discontinued treatment after 2 applications No systemic adverse effects were observed.

Certainty of the Evidence

The overall certainty of evidence for the reported outcomes for tecovirimat was **high**. The PALM007 RCT exhibited low risk of bias, with results being consistent with the conclusions of the 2 non-randomized studies. For the 2 non-randomized trials for tecovirimat, all outcomes were graded to have a very low certainty. Risk of bias was lowered to serious for time to symptom resolution and improvement because the included studies[217,218] were non-randomized with a moderate risk of bias and the potential limitations of the studies are likely to lower confidence in the estimated treatment effect. One study involving tecovirimat[217] and one study involving cidofovir[219] had low risk of bias, while one study involving tecovirimat[218] had moderate risk of bias. Issues encountered included comparability of cohorts[217,218] and adequacy of follow-up.[219]

Indirectness for change in PCR Ct outcome was graded as serious as it is not directly related to the clinical question being answered. Imprecision was graded as serious for all outcomes as the confidence intervals lie between the thresholds for recommending and not recommending treatment.

All outcomes involving cidofovir were graded to have a **very low** certainty of evidence. Imprecision was graded as serious because the one non-randomized study included[219] had a very low sample size that did not meet the criteria for optimal information size.

Other Considerations

Resource implications (Cost/cost-effectiveness)

No research evidence identified.

Stakeholder values, preferences, and acceptability

No local research evidence was identified.

A qualitative study involving 13 males in the UK found that offering tecovirimat or comparable emergency-licensed treatments for mpox is acceptable, although very few participants were aware of these treatment options. Uptake will depend on the knowledge of existing mpox treatment options and trust in the medicine and treatment provider.[221]

Equity and feasibility

Tecovirimat, brincidofovir, cidofovir, and vaccinia immunoglobulin are not listed in the Philippine FDA as a registered treatment for mpox as of June 15, 2025.

Chapter 5. Research Implications and Gaps

5.1. Limitations of the Evidence Base

While this guideline provides recommendations for various EREIDs, it also has several limitations:

- **Low to very low certainty of evidence.** The certainty of evidence is low or very low for most recommendations. This low certainty can be attributed to several factors such as the high risk of bias of included studies, indirectness of the available evidence to the guideline questions, imprecision of effect estimates, and inconsistency of findings across studies. Furthermore, most of the studies included in this review were conducted outside the Philippines, posing applicability issues within our local context.

- **Limited patient and public involvement.** The views and preferences of the target population (e.g., patients, public, etc.) were sought through the involvement of representatives of patient advocacy groups in the identification of priority EREIDs, formulation of questions, and the guideline panel discussions. Although some input from potential guideline users/implementers were obtained through the external review, we acknowledge that the opinion of other key stakeholders, including local government officials, frontliners, public health experts, and barangay health workers could have been obtained through more rigorous methods (e.g., surveys, focus group discussions).

- **Consideration of cultural factors affecting guideline implementation.** Finally, cultural factors which may affect guideline implementation such as public trust and vaccine hesitancy were rarely considered due to the paucity of local studies on patient values, preferences, and acceptability. Similarly, contextual factors affecting the applicability and feasibility of the recommendations across settings were difficult to evaluate due to limited local and contextual evidence. Future studies focused on addressing these guideline implementation concerns are recommended, as well as the inclusion of health social scientists and health economists in the guideline panel so that cultural aspects and costing issues are more thoroughly covered by the guideline.

5.2. Future Directions

To address these limitations, the following are recommended:

- **Increase local evidence.** Additional studies on emerging and re-emerging infectious diseases need to be conducted in the Philippines. These studies should be published, disseminated, and readily-available to stakeholders to guide evidence-based decision-making and practice. Future guideline development projects may also focus on searching and accessing local evidence that are not publicly available (e.g., hospital registries, health records of local government units), following ethical guidelines. Local evidence may provide more appropriate, feasible, and contextual recommendations in various settings (e.g., acceptability of vaccination for indigenous populations). Continuing disease surveillance and inclusion of robust datasets from the DOH Epidemiology Bureau and regional Centers for Health Development could better contextualize the recommendations for each EREID, pursuant to Republic Act 11332 or Mandatory Reporting of Notifiable Diseases and Health Events of Public Health Concern Act.

- **More health economic evaluation studies (e.g., cost analysis, cost-benefit, cost-effectiveness studies) are needed.** More formal studies regarding the costs of drugs, rehabilitation interventions, and diagnostic tests in the Philippines would help local government units (LGUs) plan local budgets to

facilitate the implementation of the recommendations. More LGU-oriented cost scenarios (e.g., in-kind vs cash outlays, PhilHealth coverage status) could enhance the utility of CPG recommendations. Cost-effectiveness studies in local settings may also be conducted.

- **Encourage greater participation of key stakeholders.** The participation of key stakeholders in developing and implementing guidelines needs to be strengthened. Involving patients in the creation of decision aids and educational materials will support shared decision-making. Ongoing feedback mechanisms such as online surveys or opening the CPG for public comment for a specified duration to better assess the acceptability, feasibility, and equity of recommendations from the perspective of target users. Their involvement throughout the process ensures that these guidelines are feasible and sustainable to implement in local settings.

Chapter 6. Dissemination and Implementation

6.1. Dissemination

Multiple channels will be used to disseminate the CPG for EREIDs, such as professional networks, scientific conferences, and social media. The CPG will be submitted to the DOH for adaptation and uploading on the DOH Compendium of CPGs website (https://doh.gov.ph/dpcb/doh-approved-cpg/). The CPG recommendations will likewise be forwarded to infectious disease societies such as Philippine Society for Microbiology and Infectious Diseases (PSMID) and Pediatric Infectious Disease Society of the Philippines (PIDSP) for uploading on the society websites. Adding our recommendations on COVID-19-related topics to the existing Philippine COVID-19 Living Recommendations (https://www.psmid.org/philippine-covid-19-living-recommendations-3/) may enhance uptake. A manuscript containing the CPG development process and recommendations will be submitted for publication in a local peer-reviewed journal (Acta Medica Philippina) to ensure wider dissemination.

6.2. Implementation and Adaptation

These guidelines are intended to serve as a practical resource for healthcare providers, program managers, and policymakers to enhance preparedness, prevention, early detection, and management of these priority emerging and re-emerging infectious diseases in the Philippine setting.

The implementation of this CPG for EREID, specifically COVID-19, leptospirosis, pertussis, avian influenza, and mpox, requires careful consideration of the existing healthcare delivery context, resource availability, and potential barriers across various healthcare settings in the Philippines. To facilitate the nationwide adaptation of the newly developed CPG on emerging and re-emerging infectious diseases, implementation tools and strategies will be developed *de novo* or adapted from existing outbreak response and infection prevention resources. Protocols, algorithms, and care pathways will be designed to be context-appropriate, ensuring accessibility and practicality across diverse levels of the health system, from tertiary hospitals to rural health units and community-based facilities. The DOH, in partnership with the PSMID, PIDSP and other professional societies, will employ a comprehensive implementation and monitoring strategy that includes capacity-building, system support, and performance tracking mechanisms.

In partnership with government agencies, academic institutions, local governments, and professional societies, the DOH, PSMID and PIDSP will promote widespread dissemination and adaptation of the CPGs through medical societies, webinars, CME programs, and facility-based rollouts. Educational resources such as training modules, rapid reference guides, and presentation slides for healthcare providers will be developed. Digital platforms (interactive websites and e-learning modules) for dissemination, continuing education, and timely updates during evolving outbreaks will be utilized.

To ensure refinement and alignment with frontline needs, feedback mechanisms will be established. Feedback will be gathered through online surveys, email correspondence, and dedicated reporting forms, enabling healthcare professionals to share experiences, enablers, and challenges in its implementation. These insights will guide improvements in the guidelines and their application during real-world outbreaks.

Please refer to the Implementation Checklist (**Appendix F**) for more details on implementation strategies.

Healthcare facilities and local government units are encouraged to adapt the recommendations in ways that ensure feasibility and relevance based on their unique resources and specific contexts, provided that the core principles of the guidelines are maintained.

Chapter 7. Applicability

7.1. Facilitators to Implementation

Facilitators to the implementation of the CPG on Emerging and Re-emerging Infectious Diseases (EREID) were identified through discussions of the multidisciplinary stakeholders in the steering committee, technical working group and guideline panel. The inclusion of EREID conditions in the notifiable disease list, along with established immunization programs, particularly for pertussis, and the presence of diagnostic laboratory networks for select diseases, serve as significant enablers or facilitators for applicability of these recommendations in both community and healthcare facility settings. Ongoing health worker training initiatives and the presence of local government and community health structures further facilitate the operationalization of these recommendations. Facilitators also include strong government support for surveillance and outbreak response programs as well as availability of public funding for certain diagnostics, vaccines, and treatments.

7.2. Barriers to Implementation

Similar to the identification of facilitators, barriers were also identified during deliberations of the multidisciplinary stakeholders in the steering committee, technical working group and guideline panel. Additional barriers were pointed out by the external reviewers who represented both the academe, private health sector as well as the public health sector. Several challenges which may impact implementation were identified. These include disparities in healthcare resources across regions, particularly in geographically isolated and disadvantaged areas; limited access to confirmatory diagnostics for mpox and avian influenza; and gaps in community awareness regarding zoonotic diseases such as leptospirosis and avian influenza. Variability in vaccine coverage for pertussis and COVID-19 also present barriers to consistent guideline application. Other identified barriers include gaps in the infectious disease workforce, inconsistent availability of essential medicines and vaccines, as well as misinformation and vaccine hesitancy at the community level. Moreover, emerging outbreaks or evolving evidence for these diseases may necessitate rapid updates, posing additional implementation challenges.

7.3. Resource Considerations

Where applicable, cost implications were integrated into the guideline development process. Full implementation may require investments in capacity building, procurement of diagnostics, vaccines, and essential medicines, as well as the strengthening of outbreak preparedness and response systems. The recommendations are intended to be adaptable based on resource availability and local healthcare capacities, while maintaining alignment with national standards.

7.4. Equity Considerations

Equitable access to preventive and curative interventions wherever applicable remains a key consideration, especially for vulnerable populations such as children, the elderly, pregnant women, immunocompromised individuals, and those residing in resource-limited or disaster-prone areas.

Chapter 8. Updating

8.1. Monitoring and Evaluation

To ensure effective implementation, monitoring and evaluation mechanisms are recommended. This may be done by the DOH and other task forces. Questionnaires will be sent to relevant stakeholders (e.g., clinicians, public health units, surveillance officers, and laboratories) annually to identify best practices and gaps in the screening, diagnosis, treatment, and prevention of emerging and re-emerging infectious diseases.

Monitoring and audit of implementation and adherence to diagnostic and treatment recommendations can be done **every 2 to 3 years**. Adherence is defined as the proportion of eligible cases in which the EREID CPG recommendation was correctly applied.

For monitoring and auditing, the CPG group will use the final strength of recommendations to establish key performance indicators. Recommendations classified as *"Strong"* will serve as the primary indicators. Examples of potential indicators include:

(a) proportion of suspected avian influenza cases appropriately tested using recommended diagnostics;
(b) proportion of MIS-C and MIS-N cases diagnosed based on the recommended diagnostic criteria;
(c) proportion of long COVID cases prescribed with rehabilitative interventions;
(d) number of whole cell and acellular pertussis vaccines given; and
(e) availability and stock levels of critical medicines, diagnostics, and vaccines.

Other indicators may include vaccine coverage rates, and health outcomes such as morbidity and mortality. Integration with existing surveillance platforms and stakeholder feedback will be essential to monitor progress and inform necessary updates to the guidelines. These information plus the findings of poor adherence as well as variation in practice and unintended harms should directly inform revisions of recommendations. A more formal evaluation of guideline implementation should be synchronized with guideline review cycles every 3 to 5 years.

Specific operational definitions for key indicators will be aligned with standards embodied in the DOH Manual for Clinical Practice Guideline Development and existing surveillance frameworks. These definitions will be finalized following consultations with the DOH and relevant technical experts, given the current limited availability of local data for some of these measures.

8.2. Methods on Updating the Guideline

Regular updates to incorporate new evidence and maintain the guidelines' relevance and accuracy will be scheduled **at least every 3 to 5 years or earlier** if there is rapidly evolving evidence, significant changes in disease epidemiology, developments in diagnostics, therapeutics, and vaccines, or urgent need for policy revisions.

Continuous evidence surveillance will be undertaken through periodic searches of major databases and monitoring of regulatory advisories, local health data, and relevant international guidelines. Reports of new diagnostic tools, therapeutic agents, vaccines, or epidemiologic shifts will be systematically assessed for potential impact on existing recommendations.

When an update is deemed necessary, topics will again be prioritized according to disease burden, safety implications, potential to change practice, resource considerations, and relevance to local epidemiology. For each prioritized topic, a targeted or full systematic review will be conducted, applying standardized approaches such as

the GRADE approach to assess certainty of evidence and strength of recommendations. Updated recommendations will be developed by convening a multidisciplinary expert panel, ensuring balanced representation from clinicians, public health specialists, methodologists, policy-makers, and where feasible, patient representatives.

Proposed updates will again undergo external review and stakeholder consultation to ensure methodological rigor, contextual relevance, and acceptability. Final recommendations will be submitted to the DOH with a summary of changes and rationale documented in the updated version. Dissemination will occur through publication in peer-reviewed journals, professional society channels, and stakeholder networks. Implementation will be monitored through audit and feedback, with identified barriers and facilitators informing future revisions.

Chapter 9. References

Introduction

1. Department of Health. Epidemic-prone Disease Case Surveillance (EDCS) Morbidity Week No. 48, 2023. Department of Health. 2023. https://doh.gov.ph/health-statistics/weekly-disease-surveillance-report/
2. Department of Health. DOH Observing Pertussis Trends after increasing immunization. Department of Health. 2024. https://doh.gov.ph/press-release/doh-observing-pertussis-trends-after-increasing-immunization/
3. Montemayor MT. PH logs 65% rise in leptospirosis cases. Philippine News Agency. 2023. https://www.pna.gov.ph/articles/1206772
4. Nazir A, Oduoye MO, Uzoamaka CB, et al. Unraveling the leptospirosis epidemic: tales from the Philippine outbreak - a short communication. *Ann Med Surg (Lond)*. Feb 2024;86(2):1238-1242. doi:10.1097/MS9.0000000000001535
5. Cheng K, Wu C, Gu S, Lu Y, Wu H, Li C. WHO declares the end of the COVID-19 global health emergency: lessons and recommendations from the perspective of ChatGPT/GPT-4. *Int J Surg*. Sep 01 2023;109(9):2859-2862. doi:10.1097/JS9.0000000000000521
6. Wise J. Covid-19: WHO declares end of global health emergency. *BMJ*. May 09 2023;381:1041. doi:10.1136/bmj.p1041
7. Rosen A. What to Know About COVID FLiRT Variants. Johns Hopkins University Bloomberg School of Public Health. 2024. https://publichealth.jhu.edu/2024/what-to-know-about-covid-flirt-variants
8. Cabico GK. DOH: Philippines keeps low COVID-19 risk despite rise in cases. Philstar Global. 2024. https://www.philstar.com/headlines/2024/05/21/2356805/doh-philippines-keeps-low-covid-19-risk-despite-rise-cases
9. World Health Organization. Monkeypox. World Health Organization. 2022. https://www.who.int/emergencies/emergency-events/item/2022-e000121
10. World Health Organization. WHO Director-General declares mpox outbreak a public health emergency of international concern. World Health Organization. 2024. https://www.who.int/news/item/14-08-2024-who-director-general-declares-mpox-outbreak-a-public-health-emergency-of-international-concern
11. World Health Organization. The Philippines convenes members of its public health workforce in the first intra-action review of mpox in the Western Pacific Region. World Health Organization. 2025. https://www.who.int/westernpacific/newsroom/feature-stories/item/the-philippines-first-intra-action-review-of-mpox-in-the-western-pacific-region#:~:text=%C2%A9-,The%20Philippines%20convenes%20members%20of%20its%20public%20health%20workforce%20in,in%20the%20Western%20Pacific%20Region&text=The%20Philippines%20became%20the%20first,review%20(IAR)%20of%20mpox.
12. World Health Organization. Mpox outbreak. World Health Organization. 2024. https://www.who.int/emergencies/situations/mpox-outbreak
13. Chen X, Wang W, Wang Y, et al. Serological evidence of human infections with highly pathogenic avian influenza A(H5N1) virus: a systematic review and meta-analysis. *BMC Med*. Dec 02 2020;18(1):377. doi:10.1186/s12916-020-01836-y

14. World Health Organization. Avian Influenza Weekly Update 2024. WHO Regional Office for the Western Pacific. Accessed 2024, https://iris.who.int/handle/10665/375483

Guideline Development Methodology

15. Research Institute for Tropical Medicine, University of the Philippines Manila – National Institutes of Health – Institute of Clinical Epidemiology. Clinical Practice Guidelines on the Diagnosis, Management and Prevention of Dengue for Adult and Pediatric Filipinos in the Primary Care Setting. 2023.

16. Schünemann HJ, Wiercioch W, Brozek J, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. *J Clin Epidemiol*. Jan 2017;81:101-110. doi:10.1016/j.jclinepi.2016.09.009

17. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. Apr 2011;64(4):383-94. doi:10.1016/j.jclinepi.2010.04.026

18. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ*. Dec 14 2010;182(18):E839-42. doi:10.1503/cmaj.090449

19. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. Aug 28 2019;366:l4898. doi:10.1136/bmj.l4898

20. Wells G, Shea B, O'Connell D, et al. The Newcastle–Ottawa Scale (NOS) for Assessing the Quality of Non-Randomized Studies in Meta-Analysis. . 01/01 2000;

21. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. Oct 12 2016;355:i4919. doi:10.1136/bmj.i4919

22. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. Oct 18 2011;155(8):529-36. doi:10.7326/0003-4819-155-8-201110180-00009

23. Hultcrantz M, Rind D, Akl EA, et al. The GRADE Working Group clarifies the construct of certainty of evidence. *J Clin Epidemiol*. Jul 2017;87:4-13. doi:10.1016/j.jclinepi.2017.05.006

24. Brouwers MC, Spithoff K, Kerkvliet K, et al. Development and Validation of a Tool to Assess the Quality of Clinical Practice Guideline Recommendations. *JAMA Netw Open*. May 01 2020;3(5):e205535. doi:10.1001/jamanetworkopen.2020.5535

Guideline Question 1. Rehabilitation for Long COVID

25. Frisk B, Jürgensen M, Espehaug B, et al. A safe and effective micro-choice based rehabilitation for patients with long COVID: results from a quasi-experimental study. *Sci Rep*. Jun 09 2023;13(1):9423. doi:10.1038/s41598-023-35991-y

26. Goldenberg D. Long COVID Rehabilitation: What We Know Now. MedCentral. 2024. https://www.medcentral.com/infectious/covid/long-covid-rehabilitation-what-we-know-now

27. Elvambuena BF, Borbe JBC, Santos NJC, et al. Description of Post-discharge Outcomes of Patients with COVID-19 in a Tertiary Referral Center in the Philippines. *Acta Med Philipp*. 2024;58(10):82-92. doi:10.47895/amp.vi0.7072

28. Saloma CP, Ayes MEC, Taracatac PS, Asa MRQ. Long-term COVID-19 sequelae by Theta and SARS-CoV-2 variants in a Philippine cohort. *Front Med (Lausanne)*. 2024;11:1455729. doi:10.3389/fmed.2024.1455729

29. Deng J, Qin C, Lee M, Lee Y, You M, Liu J. Effects of rehabilitation interventions for old adults with long COVID: A systematic review and meta-analysis of randomised controlled trials. *J Glob Health*. Sep 06 2024;14:05025. doi:10.7189/jogh.14.05025

30. Zeraatkar D, Ling M, Kirsh S, et al. Interventions for the management of long covid (post-covid condition): living systematic review. *BMJ*. Nov 27 2024;387:e081318. doi:10.1136/bmj-2024-081318

31. Mooren JM, Garbsch R, Schäfer H, et al. Medical Rehabilitation of Patients with Post-COVID-19 Syndrome-A Comparison of Aerobic Interval and Continuous Training. *J Clin Med*. Oct 25 2023;12(21)doi:10.3390/jcm12216739

32. Romanet C, Wormser J, Fels A, et al. Effectiveness of exercise training on the dyspnoea of individuals with long COVID: A randomised controlled multicentre trial. *Ann Phys Rehabil Med*. Jun 2023;66(5):101765. doi:10.1016/j.rehab.2023.101765

33. McNarry MA, Berg RMG, Shelley J, et al. Inspiratory muscle training enhances recovery post-COVID-19: a randomised controlled trial. *Eur Respir J*. Oct 2022;60(4)doi:10.1183/13993003.03101-2021

34. Omarova I, Akanova A, Kurmanova A, et al. Acupuncture as an Additional Method of Rehabilitation Post-COVID-19: a randomized controlled trial. *J Pharmacopuncture*. Sep 30 2023;26(3):238-246. doi:10.3831/KPI.2023.26.3.238

35. Ali AAE, Nesreen G Algazzar, Samir A Lotfy, Abdel Wahab M Taha, Emad M. Impact Of Active Cycle Of Breathing Technique On Selected Pulmonary Outcomes In Post-COVID Syndrome Patients. *Journal of Pharmaceutical Negative Results*. 01/01 2023:710-717. doi:10.47750/pnr.2023.14.S02.87

36. Nambi G, Abdelbasset WK, Alrawaili SM, et al. Comparative effectiveness study of low versus high-intensity aerobic training with resistance training in community-dwelling older men with post-COVID 19 sarcopenia: A randomized controlled trial. *Clin Rehabil*. Jan 2022;36(1):59-68. doi:10.1177/02692155211036956

37. Kuut TA, Müller F, Csorba I, et al. Efficacy of Cognitive-Behavioral Therapy Targeting Severe Fatigue Following Coronavirus Disease 2019: Results of a Randomized Controlled Trial. *Clin Infect Dis*. Sep 11 2023;77(5):687-695. doi:10.1093/cid/ciad257

38. Samper-Pardo M, León-Herrera S, Oliván-Blázquez B, Méndez-López F, Domínguez-García M, Sánchez-Recio R. Effectiveness of a telerehabilitation intervention using ReCOVery APP of long COVID patients: a randomized, 3-month follow-up clinical trial. *Sci Rep*. May 16 2023;13(1):7943. doi:10.1038/s41598-023-35058-y

39. Toussaint LL, Bratty AJ. Amygdala and Insula Retraining (AIR) Significantly Reduces Fatigue and Increases Energy in People with Long COVID. *Evid Based Complement Alternat Med*. 2023;2023:7068326. doi:10.1155/2023/7068326

40. Santana K, França E, Sato J, et al. Non-invasive brain stimulation for fatigue in post-acute sequelae of SARS-CoV-2 (PASC). *Brain Stimul*. 2023;16(1):100-107. doi:10.1016/j.brs.2023.01.1672

41. Elbannaa R, Mogahed H, Zahran M, Mohamed E. The effect of photobiomodulation versus placebo on functional capacity and fatigability in post COVID-19 elderly. *Advances in Rehabilitation*. 2022 2022;36(3):19-25. doi:10.5114/areh.2022.119900

42. Zilberman-Itskovich S, Catalogna M, Sasson E, et al. Hyperbaric oxygen therapy improves neurocognitive functions and symptoms of post-COVID condition: randomized controlled trial. *Sci Rep*. Jul 12 2022;12(1):11252. doi:10.1038/s41598-022-15565-0

43. McGregor G, Sandhu H, Bruce J, et al. Clinical effectiveness of an online supervised group physical and mental health rehabilitation programme for adults with post-covid-19 condition (REGAIN study): multicentre randomised controlled trial. *BMJ*. Feb 07 2024;384:e076506. doi:10.1136/bmj-2023-076506

44. Isla R. Silent Battle No More: Therapy Costs for Your Mental Health. Moneymax. 2023. https://www.moneymax.ph/personal-finance/articles/cost-of-therapy-philippines

45. Medical Pinas. Behavioral Therapy Price in Philippines for Adults and Children. Medical Pinas. 2024. https://medicalpinas.com/updated-behavioral-therapy-price-for-adults-and-children/

46. Ateneo Bulatao Center. Counseling & Psychotherapy. Ateneo de Manila University. n.d. https://ateneobulataocenter.com/counseling-psychotherapy/

47. Jose R. Reyes Memorial Medical Center. Procedures. Jose R. Reyes Memorial Medical Center. n.d. https://jrrmmc.gov.ph/images/Fees_and_Charges/updated/Procedures.pdf

48. Medical Pinas. Physical Therapy (PT). Medical Pinas. 2024. https://medicalpinas.com/physical-therapy-philippines/

49. Leochico CFD, Rey-Matias BMV, Rey-Matias RR. Telerehabilitation perceptions and experiences of physiatrists in a lower-middle-income country during the COVID-19 pandemic. *PM R*. Feb 2022;14(2):210-216. doi:10.1002/pmrj.12715

50. Nwankwo H, Mason J, Underwood M, et al. Cost-effectiveness of an online supervised group physical and mental health rehabilitation programme for adults with post-COVID-19 condition after hospitalisation for COVID-19: the REGAIN RCT. *BMC Health Serv Res*. Oct 31 2024;24(1):1326. doi:10.1186/s12913-024-11679-5

51. Modesto GP, Soria AL, Oliveira LVF, et al. Cost-Utility Analysis of Supervised Inspiratory Muscle Training Added to Post-COVID Rehabilitation Program in the Public Health System of Brazil. *Int J Environ Res Public Health*. Oct 29 2024;21(11)doi:10.3390/ijerph21111434

52. Colas C, Le Berre Y, Fanget M, et al. Physical Activity in Long COVID: A Comparative Study of Exercise Rehabilitation Benefits in Patients with Long COVID, Coronary Artery Disease and Fibromyalgia. *Int J Environ Res Public Health*. Aug 03 2023;20(15)doi:10.3390/ijerph20156513

53. Ibrahim AA, Hussein HM, Ali MS, et al. A randomized controlled trial examining the impact of low vs. moderate-intensity aerobic training in post-discharge COVID-19 older subjects. *Eur Rev Med Pharmacol Sci*. May 2023;27(9):4280-4291. doi:10.26355/eurrev_202305_32338

54. van Berkel J, Lalieu RC, Joseph D, Hellemons M, Lansdorp CA. Hyperbaric Oxygen Therapy for Long COVID: 3-Month Follow up Results from a Prospective Registry of 232 patients. *medRxiv*. 2024:2024.09.02.24312948. doi:10.1101/2024.09.02.24312948

55. Oliver-Mas S, Delgado-Alonso C, Delgado-Álvarez A, et al. Transcranial direct current stimulation for post-COVID fatigue: a randomized, double-blind, controlled pilot study. *Brain Commun*. 2023;5(2):fcad117. doi:10.1093/braincomms/fcad117

56. Huerne K, Filion KB, Grad R, Ernst P, Gershon AS, Eisenberg MJ. Epidemiological and clinical perspectives of long COVID syndrome. *Am J Med Open*. Jun 2023;9:100033. doi:10.1016/j.ajmo.2023.100033

57. Berger Z, Altiery DE Jesus V, Assoumou SA, Greenhalgh T. Long COVID and Health Inequities: The Role of Primary Care. *Milbank Q*. Jun 2021;99(2):519-541. doi:10.1111/1468-0009.12505

58. Saleh SAK, Adly HM. Impact of Ambient Air Pollution Exposure on Long COVID-19 Symptoms: A Cohort Study within the Saudi Arabian Population. *Infect Dis Rep*. Oct 19 2023;15(5):642-661. doi:10.3390/idr15050060

59. Zheng C, Chen XK, Sit CH, et al. Effect of Physical Exercise-Based Rehabilitation on Long COVID: A Systematic Review and Meta-analysis. *Med Sci Sports Exerc*. Jan 01 2024;56(1):143-154. doi:10.1249/MSS.0000000000003280

60. Murphy R, Calugi S, Cooper Z, Dalle Grave R. Challenges and opportunities for enhanced cognitive behaviour therapy (CBT-E) in light of COVID-19. *Cogn Behav Therap*. 2020;13:e14. doi:10.1017/S1754470X20000161

61. Rudroff T, Rainio O, Klén R. Leveraging Artificial Intelligence to Optimize Transcranial Direct Current Stimulation for Long COVID Management: A Forward-Looking Perspective. *Brain Sci*. Aug 19 2024;14(8)doi:10.3390/brainsci14080831

62. Williams RK. The Emerging Role of Photobiomodulation in COVID-19 Therapy Part II. *Medical Research Archives; Vol 11 No 8 (2023): August Issue, Vol11, Issue 8DO - 1018103/mrav11i84028*. 08/29 2023;

Guideline Question 2. MIS-C Diagnosis

63. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. May 23 2020;395(10237):1607-1608. doi:10.1016/S0140-6736(20)31094-1

64. Freedman S, Godfred-Cato S, Gorman R, et al. Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19. World Health Organization. 2020. https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19

65. Centers for Disease Control and Prevention. MIS Case Definitions and Reporting. Centers for Disease Control and Prevention. 2024. https://www.cdc.gov/mis/hcp/case-definition-reporting/index.html

66. Royal College of Paediatrics and Child Health. Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS) - national consensus management pathway. Royal College of Paediatrics and Child Health; 2020.

67. Abbas Q, Ali H, Amjad F, et al. Clinical presentation, diagnosis and management of multisystem inflammatory syndrome in children (MIS-C): a systematic review. *BMJ Paediatr Open*. Jun 06 2024;8(1)doi:10.1136/bmjpo-2023-002344

68. 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*. May 2023;182(5):2283-2298. doi:10.1007/s00431-023-04906-4

Guideline Question 3. 2024–2025 COVID-19 vaccines

69. World Health Organization. Statement on the antigen composition of COVID-19 vaccines. World Health Organization. 2025. https://www.who.int/news/item/15-05-2025-statement-on-the-antigen-composition-of-covid-19-vaccines#:~:text=The%20WHO%20Technical%20Advisory%20Group,a%20suitable%20alternative%20vaccine%20antigen.

70. World Health Organization. Tracking SARS-CoV-2 variants World Health Organization. 2025. https://www.who.int/activities/tracking-SARS-CoV-2-variants

71. President of the Philippines. Proclamation No. 297, s. 2023. Official Gazette. 2023. https://www.officialgazette.gov.ph/2023/07/21/proclamation-no-297-s-2023/

72. Department of Health. COVID-19 case tracker. Department of Health. 2025. https://doh.gov.ph/diseases/covid-19/covid-19-case-tracker/

73. Our World in Data. Philippines: Coronavirus Pandemic Country Profile. Our World in Data. 2025. https://ourworldindata.org/coronavirus/country/philippines

74. Yehoshua A, Di Fusco M, Rudolph AE, et al. Public health and economic impact of COVID-19 vaccination with the Pfizer-BioNTech COVID-19 Vaccine, KP.2, among adults in 2024/2025 in the United States. *J Med Econ*. 2024;27(1):1569-1582. doi:10.1080/13696998.2024.2429335

75. Kohli M, Maschio M, Lee A, et al. The potential clinical impact and cost-effectiveness of the updated COVID-19 mRNA Autumn 2024 vaccines in the United Kingdom. *J Med Econ*. 2024;27(1):1359-1372. doi:10.1080/13696998.2024.2413288

76. Global Initiative on Sharing All Influenza Data. Tracking of hCoV-19 Variants. Global Initiative on Sharing All Influenza Data. 2025. https://gisaid.org/hcov19-variants/

77. Idris I, Adesola RO. Emergence and spread of JN.1 COVID-19 variant. *Bulletin of the National Research Centre*. 2024/03/05 2024;48(1):27. doi:10.1186/s42269-024-01183-5

78. Shanmugaraj B. Emergence of SARS-CoV-2 variants KP.2 and KP.3 sparks concerns: What should we do? *Health Care Sci*. Aug 2024;3(4):211-214. doi:10.1002/hcs2.110

79. Estimated Vaccine Effectiveness and Durability of Pfizer/BioNTech 2024-2025 COVID-19 Vaccine. National Library of Medicine (US). https://clinicaltrials.gov/study/NCT06703190

80. Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP). Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Updated COVID-19 vaccine (2024-2025 Formulation). Centers for Disease Control and Prevention. 2024. https://www.cdc.gov/acip/grade/covid-19-2024-2025-6-months-and-older.html

81. Public Health Agency of Canada. Summary of NACI statement of January 10, 2025: Guidance on the use of COVID-19 vaccines for 2025 to summer 2026. Public Health Agency of Canada. 2025. https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/national-advisory-committee-immunization-summary-guidance-covid-19-vaccines-2025-summer-2026.html

82. Department of Health and Aged Care. COVID-19. Department of Health and Aged Care. 2025. https://immunisationhandbook.health.gov.au/contents/vaccine-preventable-diseases/covid-19

83. Park WB, Hwang YH, Kwon KT, et al. COVID-19 Vaccination Recommendations for 2024-2025 in Korea. *Infect Chemother*. Dec 2024;56(4):453-460. doi:10.3947/ic.2024.0142

84. Health Service Executive National Immunisation Office. Clinical Guidance for COVID-19 Vaccination Health Service Executive. 2025. https://www.hse.ie/eng/health/immunisation/hcpinfo/covid19vaccineinfo4hps/clinicalguidance.pdf

85. Ständige Impfkommission am Robert-Koch-Institut. Aktualisierung der COVID-19-Impfempfehlung. Robert-Koch-Institut. 2024. https://www.unimedizin-mainz.de/fileadmin/kliniken/betriebsarzt/Dokumente/Epidemiologisches_Bulletin_Covid-19_Impfung.pdf

86. Arrazola P, Fernández Prada M, Gil Á, et al. New COVID-19 vaccination recommendations in Spain: Optimizing for next seasons. *Enferm Infecc Microbiol Clin*. Jan 2025;43(1):36-46. doi:10.1016/j.eimc.2024.08.012

87. Ministry of Health. Vaccination schedule: what changes for 2025? Ministry of Health. 2025. https://www.service-public.fr/particuliers/actualites/A16520?lang=en

88. Department of Health. Manual for Clinical Practice Guideline Development. Department of Health; 2024.

89. Link-Gelles R. Effectiveness of COVID-19 vaccines. Centers for Disease Control and Prevention. 2024. https://www.cdc.gov/acip/downloads/slides-2024-10-23-24/04-COVID-Link-Gelles-508.pdf

90. Centers for Disease Control and Prevention. Current CDC Vaccine Price List. Centers for Disease Control and Prevention. 2025. https://www.cdc.gov/vaccines-for-children/php/awardees/current-cdc-vaccine-price-list.html

91. Clarke J. Who can get a Covid booster this spring and what do private jabs cost? BBC. 2025. https://www.bbc.com/news/health-55045639

92. Banks C, Estanislao RD, De Los Reyes SJ, et al. The Cost of Delivering COVID-19 Vaccines in the Philippines. Thinkwell; 2023.

93. Commission on Audit. COVID-19 National Vaccination Program. Commission on Audit. 2024. https://www.coa.gov.ph/reports/performance-audit-reports/2024-2/covid-19-national-vaccination-program/

94. Tejero LMS, Seva RR, Petelo Ilagan BJ, Almajose KL. Determinants of COVID-19 vaccination decision among Filipino adults. *BMC Public Health*. May 10 2023;23(1):851. doi:10.1186/s12889-023-15712-w

95. Mendoza RU, Dayrit MM, Alfonso CR, Ong MMA. Public trust and the COVID-19 vaccination campaign: lessons from the Philippines as it emerges from the Dengvaxia controversy. *Int J Health Plann Manage*. Nov 2021;36(6):2048-2055. doi:10.1002/hpm.3297

96. Landicho-Guevarra J, Reñosa MDC, Wachinger J, et al. Scared, powerless, insulted and embarrassed: hesitancy towards vaccines among caregivers in Cavite Province, the Philippines. *BMJ Glob Health*. Sep 2021;6(9)doi:10.1136/bmjgh-2021-006529

97. Celeste J, Sevilleja JE, Bongolan VP, Rivera RL, Caoili SE, de Castro R. COVID-19 mortality in the Philippines: a province-level analysis, 2020-2023. *medRxiv*. 2024:2024.03.14.24304321. doi:10.1101/2024.03.14.24304321

98. Statista. Number of COVID-19 vaccine doses administered in the Philippines as of March 16, 2023, by region. Statista. 2023. https://www.statista.com/statistics/1248270/philippines-coronavirus-covid19-vaccine-rollout-by-region/

99. Zhao J, Wu S, Rafal RA, et al. Vaccine equity implementation: exploring factors influencing COVID-19 vaccine delivery in the Philippines from an equity lens. *BMC Public Health*. Nov 05 2024;24(1):3058. doi:10.1186/s12889-024-20578-7

100. Lava JB, Claro V, Quiñon MS, et al. Integrating COVID-19 Vaccination in Primary Care Service Delivery: Insights From Implementation Research in the Philippines. *Glob Health Sci Pract*. Feb 20 2024;12(Suppl 1)doi:10.9745/GHSP-D-23-00202

101. Centers for Disease Control and Prevention. Moderna COVID-19 Vaccine Storage and Handling Summary. Centers for Disease Control and Prevention. 2023. https://www.cdc.gov/vaccines/covid-19/info-by-product/moderna/downloads/storage-summary.pdf

102. Pfizer Prime. Reservations available for 2025-2026 formula COVID-19 vaccines by BioNTech and Pfizer. Pfizer. n.d. https://www.primevaccines.pfizer.com/vaccine/en/USD/

Guideline Question 4. Alternative Leptospirosis Prophylaxis

103. Department of Health. National Antibiotic Guidelines. Department of Health; 2018.

104. Rajapakse S. Leptospirosis: clinical aspects. *Clin Med (Lond)*. Jan 2022;22(1):14-17. doi:10.7861/clinmed.2021-0784

105. Petakh P, Behzadi P, Oksenych V, Kamyshnyi O. Current treatment options for leptospirosis: a mini-review. *Front Microbiol*. 2024;15:1403765. doi:10.3389/fmicb.2024.1403765

106. Atherstone CJ, Stoddard RA. CDC Yellow Book: Health Information for International Travel. Centers for Disease Control and Prevention. 2025. https://www.cdc.gov/yellow-book/hcp/travel-associated-infections-diseases/leptospirosis.html

107. Guzmán Pérez M, Blanch Sancho JJ, Segura Luque JC, Mateos Rodriguez F, Martínez Alfaro E, Solís García Del Pozo J. Current Evidence on the Antimicrobial Treatment and Chemoprophylaxis of Human Leptospirosis: A Meta-Analysis. *Pathogens*. Sep 02 2021;10(9)doi:10.3390/pathogens10091125

108. Lane AB, Dore MM. Leptospirosis: A clinical review of evidence based diagnosis, treatment and prevention. *World Journal of Clinical Infectious Diseases*. 2016;6(4):61-66. doi:10.5495/wjcid.v6.i4.61

109. Gonsalez CR, Casseb J, Monteiro FG, et al. Use of doxycycline for leptospirosis after high-risk exposure in São Paulo, Brazil. *Rev Inst Med Trop Sao Paulo*. 1998;40(1):59-61. doi:10.1590/s0036-46651998000100012

110. Illangasekera VL, Kularatne SA, Kumarasiri PV, Pussepitiya D, Premaratne MD. Is oral penicillin an effective chemoprophylaxis against leptospirosis? A placebo controlled field study in the Kandy District, Sri Lanka. *Southeast Asian J Trop Med Public Health*. Sep 2008;39(5):882-4.

111. Sehgal SC, Sugunan AP, Murhekar MV, Sharma S, Vijayachari P. Randomized controlled trial of doxycycline prophylaxis against leptospirosis in an endemic area. *Int J Antimicrob Agents*. Feb 2000;13(4):249-55. doi:10.1016/s0924-8579(99)00134-x

112. Takafuji ET, Kirkpatrick JW, Miller RN, et al. An efficacy trial of doxycycline chemoprophylaxis against leptospirosis. *N Engl J Med*. Feb 23 1984;310(8):497-500. doi:10.1056/NEJM198402233100805

113. Chusri S, McNeil EB, Hortiwakul T, et al. Single dosage of doxycycline for prophylaxis against leptospiral infection and leptospirosis during urban flooding in southern Thailand: a non-randomized controlled trial. *J Infect Chemother*. Nov 2014;20(11):709-15. doi:10.1016/j.jiac.2014.07.016

114. Alikhani A, Salehifar E, Zameni F, et al. Comparison of azithromycin vs doxycycline prophylaxis in leptospirosis, A randomized double blind placebo-controlled trial. *J Infect Dev Ctries*. Nov 30 2018;12(11):991-995. doi:10.3855/jidc.10126

115. Department of Health. 2024 Drug Price Reference Index. Department of Health. 2024. https://dpri.doh.gov.ph

116. Galloway RL, Levett PN, Tumeh JW, Flowers CR. Assessing cost effectiveness of empirical and prophylactic therapy for managing leptospirosis outbreaks. *Epidemiol Infect*. Sep 2009;137(9):1323-32. doi:10.1017/S0950268808001751

117. Arbiol J, Orencio PM, Romena N, Nomura H, Takahashi Y, Yabe M. Knowledge, Attitude and Practices towards Leptospirosis among Lakeshore Communities of Calamba and Los Baños, Laguna, Philippines. *Agriculture*. 2016;6(2). doi:10.3390/agriculture6020018

118. Palatino MC, Lim PAC, Reyes MBS, Lim RJL, Vasquez DJV. 093: ASSOCIATION BETWEEN LEPTOSPIROSIS-RELATED KNOWLEDGE AND PRACTICES OF MALE PEDICAB DRIVERS IN SOME AREAS IN MANILA CITY. *BMJ Open*. 2015;5(Suppl 1):bmjopen-2015-forum2015abstracts.93. doi:10.1136/bmjopen-2015-forum2015abstracts.93

Guideline Question 5. Leptospirosis Prophylaxis for Children and Pregnant Women

119. Ombay G. DOH assures doxycycline supply amid rising leptospirosis cases. GMA News Online. 2024. https://www.gmanetwork.com/news/topstories/ nation/916716/doh-assures-doxycycline-supply-amid-rising-leptospirosis-cases/story/

120. Montemayor MT. DOH: Clearance of 1M capsules for prophylaxis expedited by FDA. Philippine News Agency. 2024. https://www.pna.gov.ph/articles/1229864

121. Department of Health. Field Health Services Information System (FHSIS) Annual Report 2023. Department of Health; 2023.

122. Cabada MM, Fischer PR, White Jr. AC. Foodborne Trematodes. In: Cherry JE, Harrison GJ, Kaplan SL, Steinback WJ, Hotez JP, eds. *Feigin and Cherry's Textbook of Pediatric Infectious Disease*. 8th Ed. ed. Elsevier; 2018.

123. *The Harriet Lane Handbook*. 23rd ed. Elsevier; 2023.

124. Supe A, Khetarpal M, Naik S, Keskar P. Leptospirosis following heavy rains in 2017 in Mumbai: Report of large-scale community chemoprophylaxis. *Natl Med J India*. 2018;31(1):19-21. doi:10.4103/0970-258X.243407

125. Dechet AM, Parsons M, Rambaran M, et al. Leptospirosis outbreak following severe flooding: a rapid assessment and mass prophylaxis campaign; Guyana, January-February 2005. *PLoS One*. 2012;7(7):e39672. doi:10.1371/journal.pone.0039672

126. Centers for Disease Control and Prevention. Leptospirosis Fact Sheet for Clinicians. Centers for Disease Control and Prevention. 2018. https://www.cdc.gov/leptospirosis/pdf/fs-leptospirosis-clinicians-eng-508.pdf

127. Barcellos C, Sabroza PC. Socio-environmental determinants of the leptospirosis outbreak of 1996 in western Rio de Janeiro: a geographical approach. *Int J Environ Health Res*. Dec 2000;10(4):301-13. doi:10.1080/0960312002001500

Guideline Question 6. Steroids, Cyclophosphamide, or Combination for Severe Leptospirosis

128. PhilHealth. Policy Recommendations on the Diagnosis, Management and Prevention of Leptospirosis. Department of Health. 2012. https://www.philhealth.gov.ph/partners/providers/pdf/Leptospirosis_Policy_Statements.pdf

129. Ramamoorthy S, Cidlowski JA. Corticosteroids: Mechanisms of Action in Health and Disease. *Rheum Dis Clin North Am*. Feb 2016;42(1):15-31, vii. doi:10.1016/j.rdc.2015.08.002

130. Kapugi M, Cunningham K. Corticosteroids. *Orthop Nurs*. 2019;38(5):336-339. doi:10.1097/NOR.0000000000000595

131. Ogino M, Tadi P. Cyclophosphamide. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK553087/

132. Cagliero J, Villanueva SYAM, Matsui M. Leptospirosis Pathophysiology: Into the Storm of Cytokines. *Front Cell Infect Microbiol*. 2018;8:204. doi:10.3389/fcimb.2018.00204

133. Philippine Society for Microbiology and Infectious Diseases. Clinical Practice Guidelines for Leptospirosis. Philippine Society for Microbiology and Infectious Diseases; 2010.

134. Pediatric Infectious Disease Society of the Philippines. Clinical Practice Guidelines on Leptospirosis in Children. Pediatric Infectious Disease Society of the Philippines; 2019.

135. Alian S, Asghari H, Najafi N, Davoudi A, Yazdani J. Corticosteroid in the treatment of moderate to severe thrombocytopenia due to leptospirosis. *Iran Red Crescent Med J*. Oct 2014;16(10):e16030. doi:10.5812/ircmj.16030

136. Southstar Drug. Southstar Drug. n.d. https://southstardrug.com.ph

Guideline Question 7. Acellular Pertussis Vaccines

137. World Health Organization. Pertussis. World Health Organization. n.d. https://www.who.int/health-topics/pertussis

138. Nie Y, Zhang Y, Yang Z, et al. Global burden of pertussis in 204 countries and territories, from 1990 to 2019: results from the Global Burden of Disease Study 2019. *BMC Public Health*. May 30 2024;24(1):1453. doi:10.1186/s12889-024-18968-y

139. Montemayor MT. DOH reports 568 pertussis cases, 40 deaths from Jan.1-March 16. Philippine News Agency. 2024. https://www.pna.gov.ph/articles/1221651

140. Liang JL, Tiwari T, Moro P, et al. Prevention of Pertussis, Tetanus, and Diphtheria with Vaccines in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. Apr 27 2018;67(2):1-44. doi:10.15585/mmwr.rr6702a1

141. Greco D, Salmaso S, Mastrantonio P, et al. A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. Progetto Pertosse Working Group. *N Engl J Med*. Feb 08 1996;334(6):341-8. doi:10.1056/NEJM199602083340601

142. Olin P, Rasmussen F, Gustafsson L, Hallander HO, Heijbel H. Randomised controlled trial of two-component, three-component, and five-component acellular pertussis vaccines compared with whole-cell pertussis vaccine. Ad Hoc Group for the Study of Pertussis Vaccines. *Lancet*. Nov 29 1997;350(9091):1569-77. doi:10.1016/s0140-6736(97)06508-2

143. Simondon F, Preziosi MP, Yam A, et al. A randomized double-blind trial comparing a two-component acellular to a whole-cell pertussis vaccine in Senegal. *Vaccine*. Oct 1997;15(15):1606-12. doi:10.1016/s0264-410x(97)00100-x

144. Gustafsson L, Hallander HO, Olin P, Reizenstein E, Storsaeter J. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. *N Engl J Med*. Feb 08 1996;334(6):349-55. doi:10.1056/NEJM199602083340602

145. Geier DA, Geier MR. An evaluation of serious neurological disorders following immunization: a comparison of whole-cell pertussis and acellular pertussis vaccines. *Brain Dev*. Aug 2004;26(5):296-300. doi:10.1016/S0387-7604(03)00169-4

146. MIMS. Tetraxim. MIMS. n.d. https://www.mims.com/philippines/drug/info/tetraxim

147. Department of Health. Expanded Program on Immunization. Department of Health. n.d. https://doh.gov.ph/uhc/health-programs/expanded-program-on-immunization/

148. Pediatric Infectious Disease Society of the Philippines PPS, Philippine Foundation for Vaccination. Childhood Immunization Schedule 2025. Pediatric Infectious Disease Society of the Philippines. 2025. https://www.pidsphil.org/home/wp-content/uploads/2024/11/2025-PIDSP-Immunization-Calendar.pdf

149. Iskedjian M, De Serres G, Einarson TR, Walker JH. Economic impact of the introduction of an acellular pertussis vaccine in Canada: a 6-year analysis. *Vaccine*. Jan 08 2010;28(3):714-23. doi:10.1016/j.vaccine.2009.10.079

150. Halperin BA, Eastwood BJ, Halperin SA. Comparison of parental and health care professional preferences for the acellular or whole cell pertussis vaccine. *Pediatr Infect Dis J*. Feb 1998;17(2):103-9. doi:10.1097/00006454-199802000-00005

151. Xu Y, Chen H, Wang B, et al. Immunogenicity and safety of concomitant administration of the sabin-strain-based inactivated poliovirus vaccine, the diphtheria-tetanus-acellular pertussis vaccine, and measles-mumps-rubella vaccine to healthy infants aged 18 months in China. *Int J Infect Dis*. Dec 2023;137:9-15. doi:10.1016/j.ijid.2023.10.006

152. Sun X, Xu Y, Tang F, et al. Immunogenicity and safety of concomitant administration of the chinese inactivated poliovirus vaccine with the diphtheria-tetanus-acellular pertussis (DTaP) vaccine in children: A multicenter, randomized, non-inferiority, controlled trial. *Front Immunol*. 2022;13:905634. doi:10.3389/fimmu.2022.905634

153. Romanenko V, Osipova I, Galustyan A, et al. Immunogenicity and safety of a combined DTPa-IPV/Hib vaccine administered as a three-dose primary vaccination course and a booster dose in healthy children in Russia: a phase III, non-randomized, open-label study. *Hum Vaccin Immunother*. Sep 01 2020;16(9):2265-2273. doi:10.1080/21645515.2020.1720437

154. Nakayama T, Vidor E, Tsuzuki D, et al. Immunogenicity and safety of a DTaP-IPV/Hib pentavalent vaccine given as primary and booster vaccinations in healthy infants and toddlers in Japan. *J Infect Chemother*. Jul 2020;26(7):651-659. doi:10.1016/j.jiac.2019.11.012

155. Pérez Chacón G, Estcourt MJ, Totterdell J, et al. Immunogenicity, reactogenicity, and IgE-mediated immune responses of a mixed whole-cell and acellular pertussis vaccine schedule in Australian infants: A randomised, double-blind, noninferiority trial. *PLoS Med*. Jun 2024;21(6):e1004414. doi:10.1371/journal.pmed.1004414

Guideline Question 8. Avian Influenza Diagnostics

156. Kenney SP. Highly Pathogenic Avian Influenza. Ohio State University. 2022. https://ohioline.osu.edu/factsheet/vme-1037

157. Dudley JP, Mackay IM. Age-specific and sex-specific morbidity and mortality from avian influenza A(H7N9). *J Clin Virol*. Nov 2013;58(3):568-70. doi:10.1016/j.jcv.2013.09.004

158. Bureau of Animal Industry. Avian Influenza. Department of Agriculture. 2025. https://www.bai.gov.ph/Report/Avian

159. Chen Y, Wang D, Zheng S, et al. Rapid diagnostic tests for identifying avian influenza A(H7N9) virus in clinical samples. *Emerg Infect Dis*. Jan 2015;21(1):87-90. doi:10.3201/eid2101.140247

160. Choi JH, Kim MS, Lee JY, et al. Development and evaluation of multiplex real-time RT-PCR assays for seasonal, pandemic A/H1pdm09 and avian A/H5 influenza viruses detection. *J Microbiol*. Apr 2013;51(2):252-7. doi:10.1007/s12275-013-2452-y

161. Apisarnthanarak A, Puthavathana P, Kitphati R, et al. Avian influenza H5N1 screening of intensive care unit patients with community-acquired pneumonia. *Emerg Infect Dis*. Nov 2006;12(11):1766-9. doi:10.3201/eid1211.060443

162. Teus MAS. *A comparative study on the effectiveness of lecture versus flyer in improving the knowledge, attitudes and practices of commercial poultry handlers regarding avian influenza in selected barangays in Zamboanga City*. Ateneo de Zamboanga University; 2006. https://www.herdin.ph/index.php/component/herdin/?view=research&cid=87924

163. National Center for Disease Prevention and Control. Avian and pandemic influenza preparedness. Department of Health; 2006.

164. Espallardo NL, Gavino RR, Perez JAA, Villanueva RA, Zamora PV. Avian influenza: the role of family physicians. *Filipino Family Physician*. 2006;44(3):121-126.

Guideline Question 9. Mpox Quarantine

165. World Health Organization. Mpox. World Health Organization. 2024. https://www.who.int/news-room/fact-sheets/detail/mpox

166. Center for Disease Control and Prevention. Clinical Considerations for Mpox in Immunocompromised People. Center for Disease Control and Prevention. 2024. https://www.cdc.gov/mpox/hcp/clinical-care/immunocompromised-people.html

167. World Health Organization. Global Mpox Trends. World Health Organization. 2025. https://worldhealthorg.shinyapps.io/mpx_global/

168. National Academies of Sciences Engineering and Medicine, Health and Medicine Division, Board on Population Health and Public Health Practice, Board on Health Sciences Policy, Committee on Evidence-Based Practices for Public Health Emergency Preparedness and Response. Implementing Quarantine to Reduce or Stop the Spread of a Contagious Disease. In: A D, L B, N C, eds. *Evidence-Based Practice for Public Health Emergency Preparedness and Response*. National Academies Press; 2020.

169. Department of Health and Human Services. What is the difference between isolation and quarantine? Department of Health and Human Services. 2022. https://www.hhs.gov/answers/public-health-and-safety/what-is-the-difference-between-isolation-and-quarantine/index.html

170. Ladhani SN, Aiano F, Edwards DS, et al. Very low risk of monkeypox among staff and students after exposure to a confirmed case in educational settings, England, May to July 2022. *Euro Surveill*. Oct 2022;27(40)doi:10.2807/1560-7917.ES.2022.27.40.2200734

171. Hagan LM, Beeson A, Hughes S, et al. Monkeypox Case Investigation - Cook County Jail, Chicago, Illinois, July-August 2022. *MMWR Morb Mortal Wkly Rep*. Oct 07 2022;71(40):1271-1277. doi:10.15585/mmwr.mm7140e2

172. Leandry L, Mureithi EW. An investigation on the Monkeypox virus dynamics in human and rodent populations for a deterministic mathematical model. *Informatics in Medicine Unlocked*. 2023/01/01/ 2023;41:101325. doi:https://doi.org/10.1016/j.imu.2023.101325

173. Ullah MS, Kabir KMA. Behavioral game of quarantine during the monkeypox epidemic: Analysis of deterministic and fractional order approach. *Heliyon*. 2024/03/15/ 2024;10(5):e26998. doi:https://doi.org/10.1016/j.heliyon.2024.e26998

174. Savinkina A, Chitwood M, Kwon J, Pitzer VE, Gonsalves G, Paltiel AD. Planning for Mpox on a College Campus: A Model-Based Decision-Support Tool. *Ann Intern Med*. Mar 2023;176(3):340-347. doi:10.7326/M22-2734

175. Deng X, Tian Y, Zou J, Yang J, Sun K, Yu H. The risk of mpox importation and subsequent outbreak potential in Chinese mainland: a retrospective statistical modelling study. *Infect Dis Poverty*. Feb 29 2024;13(1):21. doi:10.1186/s40249-024-01189-1

176. Alshahrani A. The expected economic burden on the healthcare system because of quarantining patients with monkeypox virus. *Saudi Med J*. Mar 2023;44(3):231-236. doi:10.15537/smj.2023.44.3.20220515

177. United Kingdom Health Security Agency. Adherence and barriers to following isolation guidance for mpox (monkeypox): a rapid review. United Kingdom Health Security Agency. 2022. https://assets.publishing.service.gov.uk/media/678a5f32976cb51ae15735ba/Adherence-and-barriers-to-following-isolation-guidance-for-mpox-a-rapid-review.pdf

178. Zalsos TM, Siangco H, Vallesteros L, Ochoa M. Extent of Health Care Practices and Attitude of Senior Citizens Towards Enhanced Community Quarantine in a Selected Barangay in Manila, Philippines. *PWU Research Journal*. 2021;8(1)

179. Rosali LJD, Dicto PJ, Erojo K. Gains and losses: a phenomenographic study on adolescents' understanding of isolation due to COVID-19. *Mental Health and Social Inclusion*. 2024/11/12/ 2024;29(3):278-287. doi:https://doi.org/10.1108/MHSI-06-2024-0098

180. Estrada Alvarez JM, Acuña MH, García Arias HF, Alvarado FEP, Ospina Ramírez JJ. Estimation of Incubation Period of Mpox during 2022 Outbreak in Pereira, Colombia. *Emerg Infect Dis*. Jan 2024;30(1):180-182. doi:10.3201/eid3001.221663

181. Brosius I, Van Dijck C, Coppens J, et al. Presymptomatic viral shedding in high-risk mpox contacts: A prospective cohort study. *J Med Virol*. May 2023;95(5):e28769. doi:10.1002/jmv.28769

182. Guzzetta G, Mammone A, Ferraro F, et al. Early Estimates of Monkeypox Incubation Period, Generation Time, and Reproduction Number, Italy, May-June 2022. *Emerg Infect Dis*. Oct 2022;28(10):2078-2081. doi:10.3201/eid2810.221126

183. McFarland SE, Marcus U, Hemmers L, et al. Estimated incubation period distributions of mpox using cases from two international European festivals and outbreaks in a club in Berlin, May to June 2022. *Euro Surveill*. Jul 2023;28(27)doi:10.2807/1560-7917.ES.2023.28.27.2200806

184. Miura F, van Ewijk CE, Backer JA, et al. Estimated incubation period for monkeypox cases confirmed in the Netherlands, May 2022. *Euro Surveill*. Jun 2022;27(24)doi:10.2807/1560-7917.ES.2022.27.24.2200448

185. Ward T, Christie R, Paton RS, Cumming F, Overton CE. Transmission dynamics of monkeypox in the United Kingdom: contact tracing study. *BMJ*. Nov 02 2022;379:e073153. doi:10.1136/bmj-2022-073153

186. Lim CK, McKenzie C, Deerain J, et al. Correlation between monkeypox viral load and infectious virus in clinical specimens. *J Clin Virol*. Apr 2023;161:105421. doi:10.1016/j.jcv.2023.105421

187. Piralla A, Mileto D, Rizzo A, et al. Dynamics of viral DNA shedding and culture viral DNA positivity in different clinical samples collected during the 2022 mpox outbreak in Lombardy, Italy. *Travel Med Infect Dis*. 2024;59:102698. doi:10.1016/j.tmaid.2024.102698

Guideline Question 10. Mpox Vaccination for High-Risk Individuals

188. Bragazzi NL, Kong JD, Mahroum N, et al. Epidemiological trends and clinical features of the ongoing monkeypox epidemic: A preliminary pooled data analysis and literature review. *J Med Virol*. Jan 2023;95(1):e27931. doi:10.1002/jmv.27931

189. Mitjà O, Ogoina D, Titanji BK, et al. Monkeypox. *Lancet*. Jan 07 2023;401(10370):60-74. doi:10.1016/S0140-6736(22)02075-X

190. Sudarmaji N, Kifli N, Hermansyah A, Yeoh SF, Goh BH, Ming LC. Prevention and Treatment of Monkeypox: A Systematic Review of Preclinical Studies. *Viruses*. Nov 11 2022;14(11)doi:10.3390/v14112496

191. Sah R, Paul D, Mohanty A, Shah A, Mohanasundaram AS, Padhi BK. Monkeypox (Mpox) vaccines and their side effects: the other side of the coin. *Int J Surg*. Feb 01 2023;109(2):215-217. doi:10.1097/JS9.0000000000000142

192. Farrar JL, Lewis NM, Houck K, et al. Demographic and Clinical Characteristics of Mpox in Persons Who Had Previously Received 1 Dose of JYNNEOS Vaccine and in Unvaccinated Persons - 29 U.S. Jurisdictions, May 22-September 3, 2022. *Am J Transplant*. Feb 2023;23(2):298-303. doi:10.1016/j.ajt.2023.01.003

193. Merad Y, Gaymard A, Cotte L, et al. Outcomes of post-exposure vaccination by modified vaccinia Ankara to prevent mpox (formerly monkeypox): a retrospective observational study in Lyon, France, June to August 2022. *Euro Surveill*. Dec 2022;27(50)doi:10.2807/1560-7917.ES.2022.27.50.2200882

194. Payne AB, Ray LC, Cole MM, et al. Reduced Risk for Mpox After Receipt of 1 or 2 Doses of JYNNEOS Vaccine Compared with Risk Among Unvaccinated Persons - 43 U.S. Jurisdictions, July 31-October 1, 2022. *MMWR Morb Mortal Wkly Rep*. Dec 09 2022;71(49):1560-1564. doi:10.15585/mmwr.mm7149a5

195. Thy M, Peiffer-Smadja N, Mailhe M, et al. Breakthrough Infections after Postexposure Vaccination against Mpox. *N Engl J Med*. Dec 29 2022;387(26):2477-2479. doi:10.1056/NEJMc2211944

196. Dalton AF, Diallo AO, Chard AN, et al. Estimated Effectiveness of JYNNEOS Vaccine in Preventing Mpox: A Multijurisdictional Case-Control Study - United States, August 19, 2022-March 31, 2023. *MMWR Morb Mortal Wkly Rep*. May 19 2023;72(20):553-558. doi:10.15585/mmwr.mm7220a3

197. Deputy NP, Deckert J, Chard AN, et al. Vaccine Effectiveness of JYNNEOS against Mpox Disease in the United States. *N Engl J Med*. Jun 29 2023;388(26):2434-2443. doi:10.1056/NEJMoa2215201

198. Faherty EAG, Teran RA, Black SR, et al. Mpox among Public Festival Attendees, Chicago, Illinois, USA, July-August 2022. *Emerg Infect Dis*. May 2023;29(5):1059-1061. doi:10.3201/eid2905.221797

199. Faherty EAG, Holly T, Ogale YP, et al. Notes from the Field: Emergence of an Mpox Cluster Primarily Affecting Persons Previously Vaccinated Against Mpox - Chicago, Illinois, March 18-June 12, 2023. *MMWR Morb Mortal Wkly Rep*. Jun 23 2023;72(25):696-698. doi:10.15585/mmwr.mm7225a6

200. Ladhani SN, Dowell AC, Jones S, et al. Early evaluation of the safety, reactogenicity, and immune response after a single dose of modified vaccinia Ankara-Bavaria Nordic vaccine against mpox in children: a national outbreak response. *Lancet Infect Dis*. Sep 2023;23(9):1042-1050. doi:10.1016/S1473-3099(23)00270-0

201. Montero Morales L, Barbas Del Buey JF, Alonso García M, et al. Post-exposure vaccine effectiveness and contact management in the mpox outbreak, Madrid, Spain, May to August 2022. *Euro Surveill*. Jun 2023;28(24)doi:10.2807/1560-7917.ES.2023.28.24.2200883

202. Ramchandani MS, Berzkalns A, Cannon CA, et al. Effectiveness of the Modified Vaccinia Ankara Vaccine Against Mpox in Men Who Have Sex With Men: A Retrospective Cohort Analysis, Seattle, Washington. *Open Forum Infect Dis*. Nov 2023;10(11):ofad528. doi:10.1093/ofid/ofad528

203. Wolff Sagy Y, Zucker R, Hammerman A, et al. Real-world effectiveness of a single dose of mpox vaccine in males. *Nat Med*. Mar 2023;29(3):748-752. doi:10.1038/s41591-023-02229-3

204. Tomita N, Terada-Hirashima J, Uemura Y, et al. An open-label, non-randomized study investigating the safety and efficacy of smallpox vaccine, LC16, as post-exposure prophylaxis for mpox. *Hum Vaccin Immunother*. Aug 01 2023;19(2):2242219. doi:10.1080/21645515.2023.2242219

205. van Ewijk CE, Smit C, Bavalia R, et al. Acceptance and timeliness of post-exposure vaccination against mpox in high-risk contacts, Amsterdam, the Netherlands, May-July 2022. *Vaccine*. Nov 13 2023;41(47):6952-6959. doi:10.1016/j.vaccine.2023.10.013

206. Brousseau N, Carazo S, Febriani Y, et al. Single-dose Effectiveness of Mpox Vaccine in Quebec, Canada: Test-negative Design With and Without Adjustment for Self-reported Exposure Risk. *Clin Infect Dis*. Feb 17 2024;78(2):461-469. doi:10.1093/cid/ciad584

207. Fontán-Vela M, Hernando V, Olmedo C, et al. Effectiveness of Modified Vaccinia Ankara-Bavaria Nordic Vaccination in a Population at High Risk of Mpox: A Spanish Cohort Study. *Clin Infect Dis*. Feb 17 2024;78(2):476-483. doi:10.1093/cid/ciad645

208. Ghosn J, Assoumou L, Ouattara M, et al. Impact of vaccination with third generation modified vaccinia Ankara and sexual behaviour on mpox incidence in men who have sex with men: analysis among participants of the ANRS-174 DOXYVAC trial. *Lancet Reg Health Eur*. Oct 2024;45:101020. doi:10.1016/j.lanepe.2024.101020

209. Navarro C, Lau C, Buchan SA, et al. Effectiveness of modified vaccinia Ankara-Bavarian Nordic vaccine against mpox infection: emulation of a target trial. *BMJ*. Sep 11 2024;386:e078243. doi:10.1136/bmj-2023-078243

210. Rosen JB, Arciuolo RJ, Pathela P, et al. JYNNEOS™ effectiveness as post-exposure prophylaxis against mpox: Challenges using real-world outbreak data. *Vaccine*. Jan 25 2024;42(3):548-555. doi:10.1016/j.vaccine.2023.12.066

211. Zhang X-S, Niyomsri S, Mandal S, et al. Cost-Effectiveness of Vaccination Strategies to Control Future Mpox Outbreaks in England. *medRxiv*. 2024:2024.08.20.24312301. doi:10.1101/2024.08.20.24312301

212. Ulloque-Badaracco JR, Alarcón-Braga EA, Hernandez-Bustamante EA, et al. Acceptance towards Monkeypox Vaccination: A Systematic Review and Meta-Analysis. *Pathogens*. Oct 28 2022;11(11)doi:10.3390/pathogens11111248

213. Zheng M, Qin C, Qian X, et al. Knowledge and vaccination acceptance toward the human monkeypox among men who have sex with men in China. *Front Public Health*. 2022;10:997637. doi:10.3389/fpubh.2022.997637

214. Strong C, Joson P, Chu IY, et al. Prioritization and barriers of mpox vaccination uptake among gay, bisexual and other men who have sex with men in Taiwan: 2023 HEART survey. *Vaccine*. Apr 19 2025;53:127059. doi:10.1016/j.vaccine.2025.127059

215. Gagneux-Brunon A, Dauby N, Launay O, Botelho-Nevers E. Attitudes towards monkeypox vaccination among healthcare workers in France and Belgium: an element of complacency? *J Hosp Infect*. Dec 2022;130:144-145. doi:10.1016/j.jhin.2022.09.010

Guideline Question 11. Mpox Treatments

216. Titanji BK, Hazra A, Zucker J. Mpox Clinical Presentation, Diagnostic Approaches, and Treatment Strategies: A Review. *JAMA*. Nov 19 2024;332(19):1652-1662. doi:10.1001/jama.2024.21091

217. Mazzotta V, Cozzi-Lepri A, Lanini S, et al. Effect of tecovirimat on healing time and viral clearance by emulation of a target trial in patients hospitalized for mpox. *J Med Virol*. Jun 2023;95(6):e28868. doi:10.1002/jmv.28868

218. Karmarkar EN, Golden MR, Kerani RP, et al. Association of Tecovirimat Therapy With Mpox Symptom Improvement: A Cross-sectional Study-King County, Washington, May-October 2022. *Open Forum Infect Dis*. Mar 2024;11(3):ofae029. doi:10.1093/ofid/ofae029

219. Sobral-Costas TG, Escudero-Tornero R, Servera-Negre G, et al. Human monkeypox outbreak: Epidemiological data and therapeutic potential of topical cidofovir in a prospective cohort study. *J Am Acad Dermatol*. May 2023;88(5):1074-1082. doi:10.1016/j.jaad.2022.10.043

220. Ali R, Alonga J, Biampata JL, et al. Tecovirimat for Clade I MPXV Infection in the Democratic Republic of Congo. *N Engl J Med*. Apr 17 2025;392(15):1484-1496. doi:10.1056/NEJMoa2412439

221. Paparini S, Hayes R, Weil B, et al. "If that would have lessened my symptoms, that would have been great...": a qualitative study about the acceptability of tecovirimat as treatment for mpox. *BMC Med*. Jan 21 2025;23(1):19. doi:10.1186/s12916-024-03840-y

Chapter 10. Appendices