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# What works in COVID-19 management: Interrogating the Evidence

PANCONF2022 Paediatric Infectious Diseases Pre-Conference Workshop

**Dr. Ombeva Malande**

Lecturer – Makerere/Egerton University

Research Associate, SMU University, Pretoria, South Africa

Vaccinologist/Senior Consultant (Paediatric infectious diseases)

Director – East Africa Centre for Vaccines and Immunization(ECAVI)

Monday, 17<sup>th</sup> January, 2022



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# COVID-19 Symptoms in children

- COVID-19 symptoms may show 2-14 days after exposure.
- We have noted higher leaning towards children with omicron than with other variants
- COVID in children tends to be mild, and largely asymptomatic
- Symptoms are usually gastrointestinal- like diarrhoea or vomiting,
- Others maybe :
  - Fever, Cough, Shortness of breath, sore throat
  - Runny or stuffy nose, Body aches, Headache, Chills, Fatigue
  - Gastrointestinal: diarrhea, nausea, Loss of smell and taste

## 1.6 Age and Sex Distribution of COVID Confirmed Cases and Deaths

One hundred and seventy-nine thousand one hundred and ninety-three (56%) are males and 138131 (44%) are females. Most of the cases; 82322 (26%), are in the age group of 30-39 years. Figure 6 below shows the age and sex distribution of COVID-19 cases.

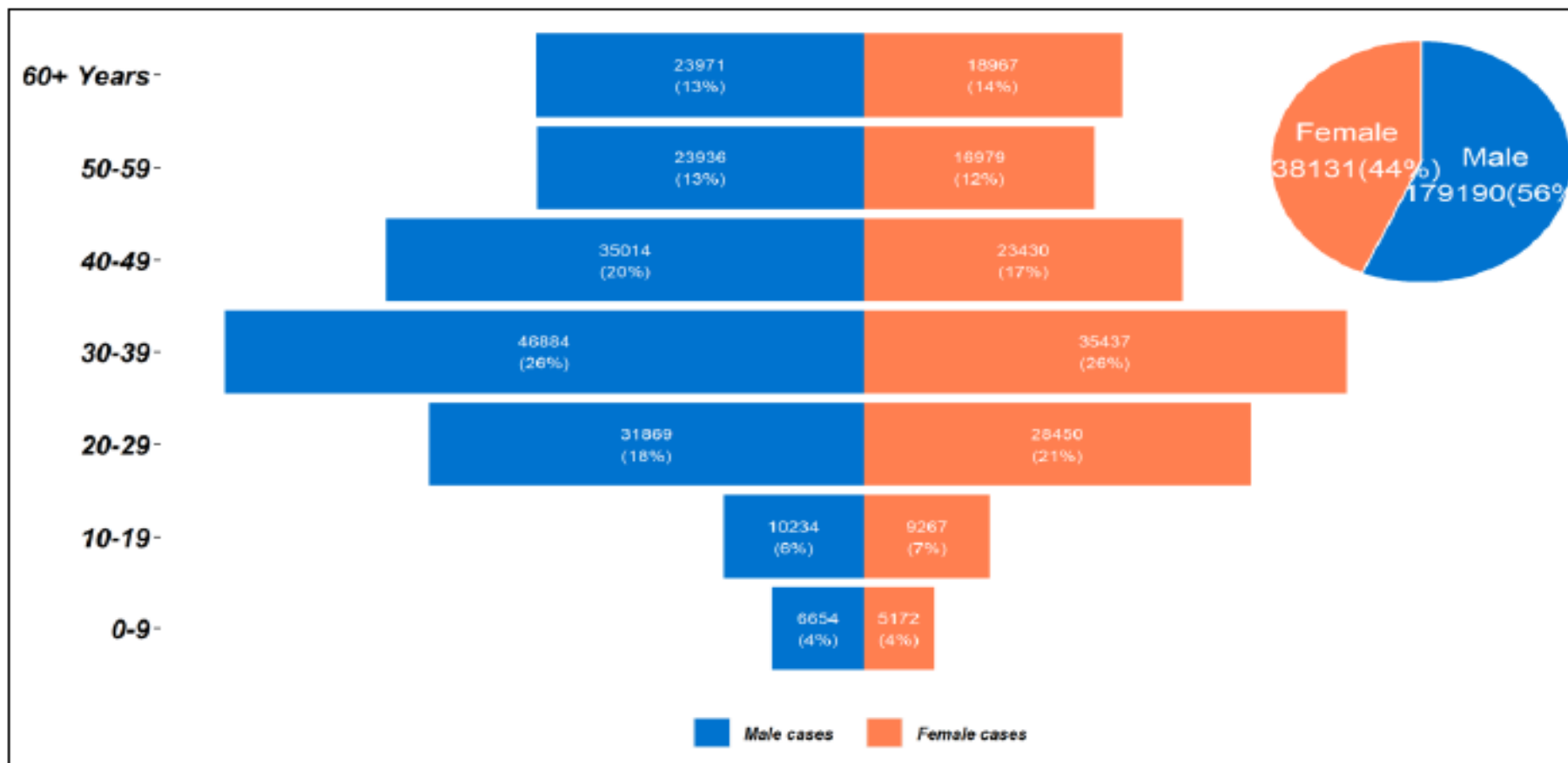


Figure 6: Age and Sex Distribution of COVID-19 Cases Kenya

# Spectrum of Pediatric Covid Cases



\*Red flag signs: Rapid breathing,  $\text{SpO}_2 < 94\%$ , fever persisting  $> 3$  days, lethargy/drowsiness, poor feeding

# Assessment of Paediatric COVID-19 Severity

Definitions of severity provided in the multicenter interim guidance on the use of antivirals for children with COVID-19 :

- Mild or moderate disease – No new or increased supplemental oxygen requirement
- Severe disease – New requirement for supplemental oxygen or increased requirement from baseline without new or increased need for ventilatory support (noninvasive or invasive)
- Critical disease – New or increased need for noninvasive or invasive mechanical ventilation, sepsis, multiorgan failure, or rapidly worsening clinical trajectory

*Chiotos K, Hayes M, Kimberlin DW, et al. Multicenter Interim Guidance on Use of Antivirals for Children With Coronavirus Disease 2019/Severe Acute Respiratory Syndrome Coronavirus 2. J Pediatric Infect Dis Soc 2021; 10:34.*

# IMNCI type approach for covid-19 in children

## ASK

Has the infant had fever, runny nose, loose stool, poor feeding

Age based Respiratory rate criteria for fast breathing

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 < 2 mo. ≥60/min 2mo-12mo: ≥ 50/min  
 12mo-5yr.: ≥40/min  
 >5 yrs.: ≥30/min

## LOOK, LISTEN, FEEL (to be done 12 hrly.)

- Count the breaths in one minute
- Repeat the count if elevated
- Look for nasal flaring
- Look for severe chest indrawing
- Look and listen for grunting
- Measure axillary temperature
- Measure oxygen level

Young infant/child must be calm

## LOOK FOR DANGER SIGNS

- See if infant/Child is lethargic or unconscious
- Look at the young infant/child's movements- are they less than normal
- Is the young infant/child unable to drink or vomits
- Dry oral mucosa/sunken eyes
- Pinch the skin of the abdomen. Does it go back:
  - Very slowly (longer than 2 sec.)
  - Slowly?
- Skin Rash, Stomach pain, red eyes, pale/grey/blue skin/Lips/Nail beds, extremely tired/lethargic/unconscious (MIS-C)

Fever, Stuffy nose +/- , normal respiration, no grunting, no chest indrawing, alert, active, Spo2 >95%

Report to CCC by telemedicine every evening  
 Reassess daily  
 Paracetamol 10-15 mg/ kg/ dose every 4-6 hrly.  
 Continue breast feeding

If progress to moderate disease i.e. fast breathing (based on provided age based cut-offs\*) and

Refer to near by CCC using ambulance equipped with Oxygen and pediatric specific monitoring equipment

No intercostal/ suprasternal/ subcostal retractions and

Should ensure the bed availability in CCC prior to shifting

Unremitting fever for >5 days (if axillary temp. 37.5C or above (or feels hot to touch)

HCW should accompany the child till CCC

Develops danger signs at any time or

Co-morbidities (underlying chronic lung/skin/liver disease, malignancy, genetic syndrome)



# Summary of observations

- ▶ Children with COVID-19 and **severe or critical** lower respiratory tract disease generally require hospital admission.
- ▶ Supportive care (eg, respiratory support, fluid and electrolyte support, monitoring for cytokine release syndrome) is the mainstay of therapy for children with severe or critical COVID-19.
- ▶ Though recommended only for RCT settings, if an antiviral therapy is required, then remdesivir is the antiviral agent of choice – since RCTs in adults suggest a potential benefit.
- ▶ There is no role for HCQ or chloroquine – the emergency use authorization has been revoked, its clinical benefit is unproven, and it has potential toxicity.

# Summary of observations

- For hospitalized children not in an RCT, use of adjunctive therapies for immune-mediated complications (eg, glucocorticoids, interleukin-6 inhibitors, convalescent plasma) of COVID-19 on a case-by-case basis.
- Children with mild symptoms (eg, fever, cough, pharyngitis, other respiratory symptoms) generally should be managed at home unless they have a chronic condition that increases their risk of severe disease.
  - Decisions regarding outpatient antiviral or monoclonal therapy are made on a case-by-case basis.
  - Additional management is focused on prevention of transmission to others (ie, isolation), monitoring for clinical deterioration (eg, difficulty breathing, cyanosis, symptoms of shock), and supportive care.
  - Prevention of transmission focuses on hygiene and social distancing.
  - Manage indirect COVID effects - adverse physical and mental health effects of prolonged home confinement (eg, decreased physical activity, poorer quality diet, social isolation, increased risk of violence).





## Consensus treatment Considerations

- Either NSAIDs or acetaminophen may be used for symptomatic treatment of pain or discomfort in children with COVID-19.
  - Initial concerns about potential negative effects of NSAIDs in patients with COVID-19 have not been supported by most observational data
  - In a meta-analysis of 11 observational studies (>683,000 participants), exposure to NSAIDs was not associated with increased risk of SARS-CoV-2 infection, severe/critical COVID-19 disease, or all-cause mortality
- The management of fever in children with COVID-19 is the same as for fever due to other infections

# Consensus treatment Considerations

- Asthma is NOT a strong risk factor for acquiring COVID-19; or increased risk of more severe disease or death in COVID
  - Poorly-controlled asthma may lead to a more complicated COVID-19 disease course, a higher rate of intubation and prolonged mechanical ventilation in adults with asthma
  - Continue recommended Rx towards good asthma control, in COVID-19
- COVID +ve children on angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) should continue treatment with these agents if there is no other reason for discontinuation (eg, hypotension, AKI).
  - This approach is supported by multiple guideline panels
  - Speculation that patients with COVID-19 who are receiving ACE inhibitors or ARBs may be at increased risk for adverse outcomes has not been supported by findings from observational studies.

# Consensus treatment Considerations

- For ISS children – need to discuss the benefits and risks of reducing immunosuppressive therapy with the prescribing specialist.
  - Relationship between immune compromise and severe COVID-19 disease has not been well established in children
  - Management of viral infections in immunocompromised hosts typically includes reduction of baseline immunosuppression, if reduction is possible.
- Recommendations for antiviral therapy for influenza infection in children are unchanged during the COVID-19 pandemic.
  - If indicated, antiviral therapy for influenza can be initiated while awaiting lab results.
  - If already initiated, antiviral therapy can be discontinued when influenza has been excluded through molecular testing.

# Consensus treatment Considerations

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# Consensus treatment Considerations for hospitalized children

- Children with COVID-19 and severe or critical lower respiratory tract disease generally require hospital admission.
- Children with nonsevere COVID-19 may require hospital admission if they are at risk for severe disease due to underlying conditions (eg, immune compromise) or are febrile infants younger than 30 days.
  - Supportive care should be provided for all pediatric patients with COVID-19 as recommended by various national committees. It is the mainstay of therapy for patients with severe or critical COVID-19.
- Most children with COVID-19 improve with supportive care, even those with severe disease

# Consensus treatment Considerations for hospitalized children

## Routine supportive care measures include:

- Provision of respiratory support, including supplemental oxygen and ventilatory support (noninvasive or invasive); **respiratory status may change suddenly after approximately one week of symptoms**
- Provision of fluid and electrolyte support.
- Provision of empiric antibiotics as indicated for community-acquired or health care-associated pneumonia; continuation of empiric antibiotics should be determined by cultures and other microbial tests and clinical condition.  
Bacterial coinfections appear to be infrequent



## Consensus treatment Considerations for hospitalized children

- Monitoring for cytokine release syndrome by monitoring blood pressure for hypotension, oxygen saturation for worsening hypoxemia, and biomarkers.
  - Obtain baseline C-reactive protein (CRP), D-dimer, ferritin, lactate dehydrogenase (LDH), and interleukin-6 (IL-6).
  - Monitor CRP, D-dimer, ferritin, and LDH two or three times per week or if there is concern for worsening disease. IL-6 is performed offsite; we repeat it twice per week if it is elevated at baseline or if there is concern for worsening disease.



## Consensus treatment Considerations for hospitalized children

- Provision of thromboprophylaxis – Interventions to reduce the risk of venous thromboembolism (VTE) may be warranted for children hospitalized with COVID-19.
  - For hospitalized children without multisystem inflammatory syndrome in children (MIS-C), make decisions about pharmacologic VTE prophylaxis on a case-by-case basis, considering other VTE risk factors and the child's risk of bleeding
  - Nonpharmacologic strategies for VTE prophylaxis (eg, intermittent pneumatic compression devices [size permitting] and early mobilization) are encouraged.



## Consensus treatment Considerations for hospitalized children

- **Retrospective study of 426 patients <21 years of age hospitalized with COVID-19**, nine (2.1 percent) had documented thrombotic events, including PE (n = 3), DVT of the upper extremity (n = 2), DVT of the lower extremity (n = 1), intracardiac thrombosis (n = 2), and cerebral sinovenous thrombosis (n = 1)
  - All of the children with thrombotic events had underlying medical conditions (cancer, obesity, congenital heart disease), & 4 were critically ill; six had a central venous catheter.
  - Seven were  $\geq 12$  years of age.
  - Markedly elevated D-dimer (ie,  $>5$  times the upper limit of normal) was a strong independent predictor of thrombosis.
  - Thrombosis was present on admission in 3 patients

## SARS-CoV-2 antiviral therapy for select patients

Antiviral therapy should be considered on a case-by-case basis and preferably occur in the context of a clinical trial, & reserved for children with documented severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection

- **Potential considerations** –disease severity, clinical trajectory, existing evidence of effectiveness, and underlying conditions that may increase the risk for progression.
- Though of unproven benefits, we suggest antiviral therapy for children with documented severe or critical COVID-19.
- Antiviral therapy also may be warranted for children with mild or mod disease and an underlying condition that increases or may increase the risk of severe disease (eg, medical complexity, congenital heart disease, among others)



# Remdesivir

- When a decision is made to use antiviral therapy in a child who cannot be enrolled in a clinical trial, we suggest remdesivir rather than other antiviral agents
- RCTs & case series in adult patients suggest that it may reduce time to recovery (particularly in patients who are not critically ill) and appears to be well tolerated
- When the supply of remdesivir is limited, it should be prioritized for patients with severe rather than critical disease (as defined above); the benefits for those with critical disease are uncertain



## Baricitinib

- It is a kinase inhibitor used for the treatment of rheumatoid arthritis.
  - An immunomodulator thought to have antiviral effects (interferes with viral entry).
  - FDA - emergency use authorization in patients  $\geq 2$  years of age who are hospitalized with COVID-19 and require oxygen or ventilatory support, or extracorporeal membrane oxygenation
- Should ideally be used in the context of a clinical trial.
- May provide a mortality benefit for select patients, - the combination of baricitinib and remdesivir appeared to modestly improve the time to recovery without increased rates of infection, VTE, or other adverse events

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## Hydroxychloroquine and chloroquine

- Not indicated for the treatment of COVID-19 in children
- Its emergency use authorization for the treatment of COVID-19 in the United States has been revoked
- Should be avoided in children with underlying QTc abnormalities and those who require other medications with potential for serious drug interactions with hydroxychloroquine.
- Its thought to alter endosomal and lysosomal pH, inhibiting viral replication and propagation, although the exact mechanism of antiviral activity remains uncertain

## Other considerations

- Lopinavir-ritonavir – Not recommended due to absence of efficacy and unfavorable pharmacodynamics
- Decisions about the use of glucocorticoids for immune-mediated complications of COVID-19 be on a case-by-case basis according to disease severity
  - Although glucocorticoids have been associated with decreased mortality in adult patients, trials in children are ongoing and the benefits and risks are uncertain.
  - For select children with severe or critical COVID-19 who cannot participate in a clinical trial (ie, those who require mechanical ventilation or those who require supplemental oxygen and have risk factors for disease progression), low-dose glucocorticoids may be warranted, the duration of therapy is up to 10 days or until discharge, whichever is shorter.



# Other considerations

- **Low-dose glucocorticoid regimens include one of the following**
  - Dexamethasone 0.15 mg/kg orally, IV, or nasogastrically (NG) once daily (maximum dose 6 mg)
  - Prednisolone 1 mg/kg orally or NG OD (maximum dose 40 mg)
  - Methylprednisolone 0.8 mg/kg IV OD (maximum dose 32 mg)
  - Hydrocortisone
    - For neonates (<1 month of age): 0.5 mg/kg IV every 12 hours for 7 days followed by 0.5 mg/kg IV once daily for 3 days
    - For children  $\geq$ 1 month: 1.3 mg/kg IV every 8 hours (maximum dose 50 mg; maximum total daily dose 150 mg)



# Other considerations

- The use of glucocorticoids is supported by RCTs comparing glucocorticoids with placebo or usual care, in adult patients with severe or critical COVID-19.
  - In a meta-analysis of 7 RCTs, (total of 1703 critically ill patients), glucocorticoids reduced 28-day all-cause mortality without increased serious adverse events
  - The results were similar with dexamethasone or hydrocortisone.
  - Another meta-analysis of RCTs comparing glucocorticoids with standard care irrespective of disease severity concluded that glucocorticoids probably reduce all-cause mortality at a median of 28 days and may increase ventilator-free days
- Although the WHO strongly recommends systemic glucocorticoids for patients with severe or critical COVID-19, they acknowledge that the applicability of the recommendation for children is uncertain because children were underrepresented in the clinical trials supporting benefit.



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## Other considerations

- Glucocorticoids plus tocilizumab — Tocilizumab is a monoclonal antibody that reduces inflammation by blocking the IL-6 receptor, used in the management of several rheumatologic conditions in children and adults
  - Has FDA emergency use authorization in hospitalized patients  $\geq 2$  years of age on systemic glucocorticoids and require supplemental oxygenation, mech vent or ECMO, there is limited benefits in children with COVID-19.
  - It should ideally be used in the context of a clinical trial.
  - Tocilizumab may reduce progression to mechanical ventilation, duration of hospitality, and mortality in adults with COVID-19, but the findings are inconsistent
  - Common adverse reactions in COVID - constipation, diarrhea, nausea, anxiety, insomnia, hypertension, and superinfection.



## Other considerations

- No routine use of other immune modulators (interferon-beta 1b, convalescent plasma from recovered COVID-19 patients) in the treatment of children with COVID-19, except in the context of a clinical trial
- There is NO available data on the use of vitamin A for the treatment of COVID-19
  - Vitamin A has long been used as an adjunctive therapy in the treatment of measles, and its use has been associated with decreased morbidity and mortality from measles-associated pneumonia.
  - Vitamin A deficiency may be associated with impairment of humoral and cell-mediated immunity, and even mild vitamin A deficiency may lead to increased morbidity from measles and other viral respiratory infections



# Other considerations

## **Outpatient monoclonal antibody therapy —**

- Not recommended for routine administration except in the context of a clinical trial and should consider risk factors supported by evidence from studies in children. Evidence from randomized trials and observational studies in adult patients suggests that outpatient monoclonal antibody therapy soon after diagnosis reduces the need for hospitalization
- Several SARS-CoV-2 variants with mutations that affect the spike protein may have reduced susceptibility to available monoclonal antibody therapies

## Multisystem inflammatory syndrome in children (MIS-C)

- (MIS-C) is an uncommon complication of COVID-19 that has a presentation similar to Kawasaki disease (KD) or toxic shock syndrome
- care is determined by the severity of illness, risk of complications, and adequacy of follow-up. Most children with MIS-C are managed in the inpatient setting
- MIS-C requires coordination of many different specialties. Infectious disease, rheumatology, and cardiology specialists should be consulted early
- Children presenting with shock should be resuscitated, focus on supportive care to maintain hemodynamic stability and ensure adequate systemic perfusion; Continuous cardiac monitoring is essential so that arrhythmias are promptly detected and treated.
- Due to septic shock and toxic shock syndrome,-like symptoms; severe cases require prompt empiric broad-spectrum antibiotic therapy pending culture results

## Multisystem inflammatory syndrome in children (MIS-C)

- Since MIS-C represents a postinfectious complication rather than active infection, the role of antiviral therapies (eg, remdesivir) in the management of MIS-C is limited.
- Immune-modifying therapies :
  - Children with moderate-to-severe manifestations –(eg, shock requiring vasopressors, left ventricular [LV] systolic dysfunction, elevated troponin or brain natriuretic peptide, arrhythmia, coronary artery [CA] aneurysm [Z-score  $\geq 2.5$ ], or other manifestations requiring PICU care), - initial therapy with combined intravenous immune globulin (IVIg) plus a glucocorticoid rather than IVIg alone . **If IVIg is not available, treatment with glucocorticoids alone is acceptable.**

# Multisystem inflammatory syndrome in children (MIS-C)

- Immune-modifying therapies :
  - Observational studies suggest that initial combination therapy may hasten cardiac recovery and reduce the need for hemodynamic support and/or adjunctive immune-modifying therapy. The dosing for IVIG in this setting is 2 g/kg administered in a single infusion over 8 to 12 hours. Glucocorticoid therapy consists of intravenous methylprednisolone at a dose of 2 mg/kg/day in two divided doses – later equiv oral dose of prednisolone or prednisone by the time of discharge and then tapered off over 2-4 weeks.
  - Children with less severe manifestations –treatment with IVIG alone initially. However, if the patient has persistent fevers and rising C-reactive protein (CRP), D-dimer, and/or ferritin despite treatment with IVIG, - add glucocorticoid therapy

## Multisystem inflammatory syndrome in children (MIS-C)

- Prevention of thrombotic complications – Patients with MIS-C are at increased risk of thrombosis. The optimal approach to thromboprophylaxis in this setting is uncertain, and practice varies considerably.
  - All patients with MIS-C – For all patients, we suggest low-dose aspirin (3 to 5 mg/kg daily) . This is based largely on indirect evidence from patients with KD.
- Role of other agents –
  - The role of other adjunctive therapies (interleukin [IL] 1 inhibitors [eg, anakinra, canakinumab], IL-6 inhibitors [eg, tocilizumab], tumor necrosis factor [TNF] inhibitors [eg, infliximab]) is uncertain. Consultation with pediatric infectious disease and rheumatology specialists is advised.

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## Home based Care for children with COVID-19

- Children with documented or suspected COVID-19 and mild symptoms (eg, fever, cough, pharyngitis, other respiratory symptoms) generally should be managed at home unless they have a chronic condition that increases their risk of severe disease.
- Management is focused on prevention of transmission to others (ie, isolation), monitoring for clinical deterioration, and supportive care.
- The clinical course for symptomatic children and adolescents may be prolonged, but specific data are lacking.
- Although few studies have evaluated the clinical course of COVID-19 in children, persistent physical symptoms (eg, fatigue, joint pain, cough) are common in adults.



## Home based Care for children with COVID-19

### Monitoring for clinical deterioration –

Caregivers of children who are managed at home should be counseled about symptoms of clinical deterioration, which may occur suddenly after approximately 1 week of symptoms & should prompt urgent re-evaluation

Manifestations of clinical deterioration include:

- Severe respiratory distress, difficulty breathing (for infants: grunting, central cyanosis, inability to breastfeed)
- Chest pain or pressure
- Blue lips or face
- Findings associated with shock (eg, cold, clammy, mottled skin; new confusion; difficulty arousing; substantially reduced urine output)
- Inability to drink or keep down any liquids

# Home based Care for children with COVID-19

## Adequate vitamin D intake —

- Adequate intake of vitamin D is necessary for bone health. Vitamin D supplementation may be necessary to meet the recommended intake, particularly for children with limited exposure to sunlight (eg, those remaining inside while self-isolating).
- However, the role of vitamin D in the treatment and prevention of COVID-19 is uncertain, and doses exceeding the upper level intake are **not** recommended
- Whether vitamin D deficiency increases the risk of SARS-CoV-2 infection in children is uncertain. The association may be confounded by other risk factors for both vitamin D def and SARS-CoV-2 infection (eg, obesity).



## Home based Care for children with COVID-19

- **Avoidance of unproven interventions** —
  - Hydroxychloroquine, ivermectin, and other investigational agents should be **AVOIDED** or used only in the context of a clinical trial;
  - Misuse of nonpharmaceutical forms of the investigational agents (eg, **chloroquine phosphate, which is used in home aquariums; ivermectin intended for animals**) may lead to severe toxicity, including death.



## Home based Care for children with COVID-19

- FOLLOW-UP is individualized according to underlying comorbidities, severity of illness, persistence of symptoms, and complications.
- Children without multisystem inflammatory syndrome in children (MIS-C) – Children with >4 days of symptoms (eg, fever, chills, myalgia, lethargy) and children who required hospitalization may require follow-up during isolation to ensure continued recovery
- All children require a follow-up visit after the isolation period is over before return to physical activity.
- The follow-up visit should address ongoing and newly developed symptoms, including cardioresp symptoms, loss of smell or taste, neurodevelopmental symptoms (eg, motor, cognitive, language impairment; inattention; memory problems), fatigue, headache, and mental health sequelae

# Home based Care for children with COVID-19

- Children with ongoing symptoms and worrisome signs should be evaluated as clinically indicated (eg, for myocarditis or MIS-C, intracranial pathology in children with headache and worrisome features)
- Otherwise, minimize diagnostic testing and provide supportive care focused on improving function (eg, by setting achievable goals) for the first 12 weeks of recovery
- Persistent symptoms may be related to SARS-CoV-2 infection, they also may be related to the conditions of the pandemic (eg, social isolation, death of a family member, trauma of hospitalization, decreased physical activity)
- R/o "post-COVID-19 condition" - physical and mental health symptoms present  $\geq 4$  weeks after SARS-CoV-2 infection (of any severity).

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## Home based Care for children with COVID-19

- Behavioral and mental health surveillance
- Guidance for return to activity (eg, school, sports, employment), including provision of support as indicated (eg, gradual return to school)
- Athletes should be evaluated by their clinician for cardiac symptoms (eg, chest pain, palpitations, syncope, shortness of breath out of proportion to respiratory tract illness) before returning to sports training, practice, or competition because of the possibility cardiac complications of SARS-CoV-2

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## Home based Care for children with COVID-19

- COVID-19 immunization (if eligible) and catch-up of routine immunizations (if necessary)
- Reinforcement of strategies to prevent infection
- Education about symptoms that should prompt re-evaluation
- Healthy habits – Adequate nighttime sleep, maintaining a consistent daily schedule, adequate hydration and nutrition, and avoidance of alcohol and drugs
- Testing for SARS-CoV-2 after recovery is not recommended unless the child or adolescent is symptomatic or has been exposed to someone recently diagnosed with SARS-CoV-2 infection. A negative SARS-CoV-2 test is not necessary to discontinue isolation.

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