Figure 3. Time course of laboratory tests for COVID-19

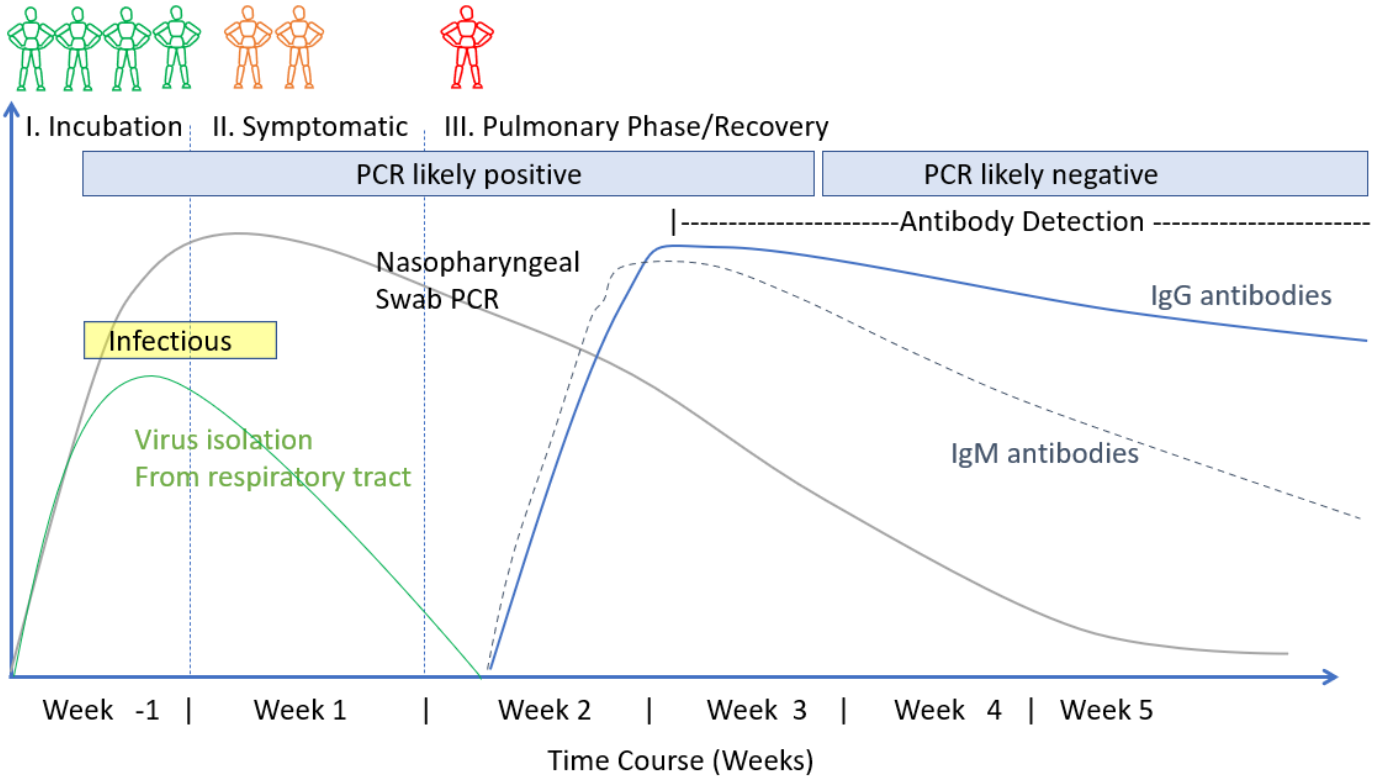
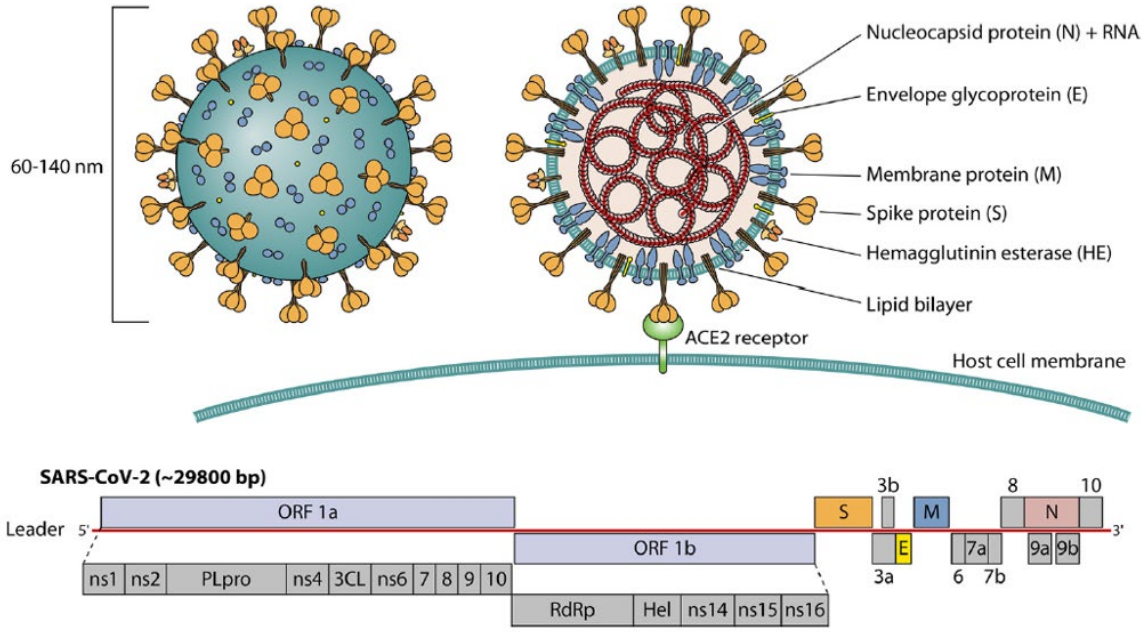


Figure 4. SARS-Co-V-2 Structure and RNA genome



1. Introduction

While there is **no cure or "Magic-bullet"** for COVID-19, recently, a number of therapeutic agents have shown great promise for both the prevention and treatment of this disease including Ivermectin, Vitamin D, quercetin, melatonin, fluvoxamine, corticosteroids, curcumin (turmeric), *Nigella sativa* and antiandrogen therapy. It is likely that no single drug will be effective in treating this complex disease and that multiple drugs with different mechanisms of action used in specific phases of the disease will be required. Furthermore, a growing body of evidence suggests that many of these agents may act synergistically in various phases of the disease. [1-3]

As the pandemic has played out over the last year over four million patients have died world-wide, and the pandemic shows no signs of abating. Most countries across the globe have limited resources to manage this humanitarian crisis. We developed the **MATH+ protocol** to provide guidance for the treatment of the pulmonary phase of this disease with the goal of reducing the hospital mortality from this devastating disease. However, it soon became obvious that our emphasis needed to shift to the prevention and early (home) treatment of this catastrophic disease to prevent patients progressing to the pulmonary phase and requiring hospitalization (see Figure 5). Hence, we developed the **I-MASK+ and the Test and Treat protocols.** While we strongly believe that such an approach can mitigate the development and progression of this disease, limit deaths, and allow the economy to re-open, "Health-Care authorities" across the globe have been silent in this regard, including the WHO, CDC, NIH, etc (see NIH Guidance, Figure 6a and 6b). While vaccination is part of the solution, it will take many months if not years to vaccinate 70-85% of the world's population of 7.8 billion people required for "herd immunity". We believe that the **I-MASK+** protocol provides a bridge to universal vaccination. Furthermore, we have developed the **I-MASS protocol** for a MASS Distribution campaign to lessen the impact of COVID-19 in resource-poor countries. Mutant strains of SARS-CoV-2 have recently appeared, these stains have demonstrated increased transmissibility.[4,5] [6] Many of these mutations involve the spike protein (against which almost all of the vaccines have targeted), raising the real possibility that the vaccines may become less effective against the mutating strains of SARS-CoV-2.[5,7,8] And, finally the Post-COVID syndrome or "long-hauler syndrome" has emerged as a common and disabling disorder its pathophysiology of which is poorly understood. We offer the **I-RECOVER** protocol to help treat this disabling disorder. Recently, the post-vaccination syndrome has emerged as a problematic entity; we believe that the **I-RECOVER** protocol has utility in treating this syndrome.

Figure 5. Treatment Phases of COVID-19

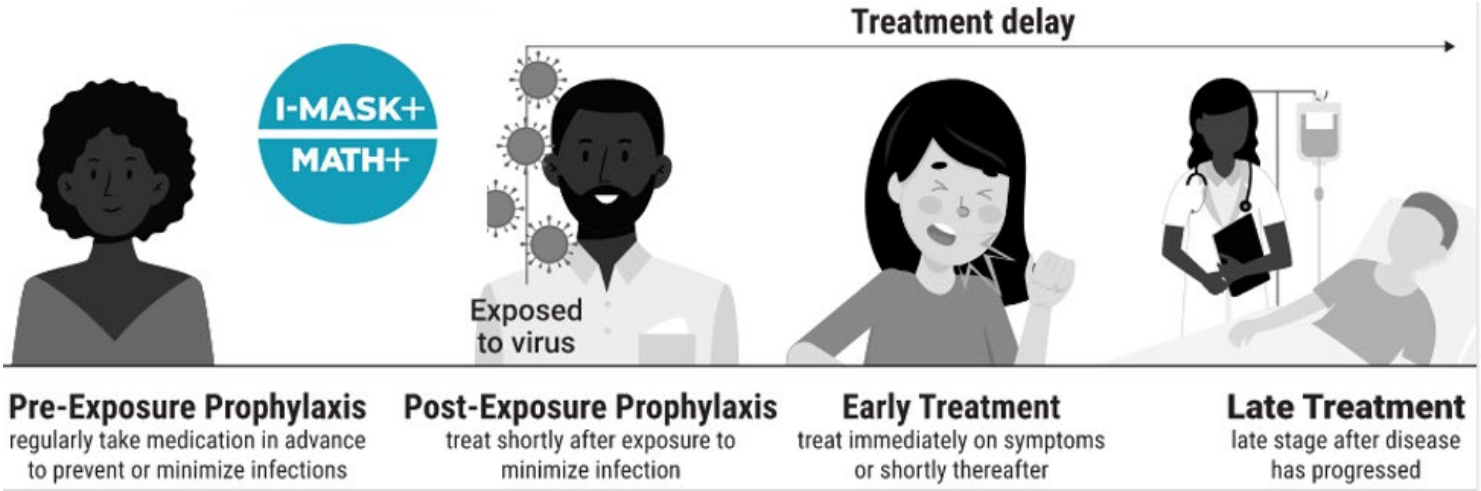


Figure 6a. NIH Recommendations for the Treatment of COVID-19 across the stages of the disease.

Clinical Management Summary

Last Updated: August 25, 2021

Figure 1. Therapeutic Management of NonHospitalized Adults With COVID-19

PATIENT DISPOSITION	PANEL'S RECOMMENDATIONS
Not Requiring Hospitalization or Supplemental Oxygen, As Determined by a Health Care Provider in ED or an In-Person or Telehealth Visit	Anti-SARS-CoV-2 monoclonal antibody products are recommended for outpatients with mild to moderate COVID-19 who are at high risk of disease progression, as defined by the EUA criteria (treatments are listed in alphabetical order):[a] • **Casirivimab plus imdevimab**; *or* • **Sotrovimab** At this time, the Panel **recommends against** the use of **bamlanivimab plus etesevimab** in these patients due to an increase in the proportion of potentially resistant variants **(AIII)**.[a] See text for details. The Panel **recommends against** the use of **dexamethasone** or **other systemic glucocorticoids** in the absence of another indication **(AIII)**.[b]

Figure 2. Therapeutic Management of Hospitalized Adults With COVID-19 Based on Disease Severity

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen	Use one of the following options: • **Remdesivir**[b] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone plus remdesivir**[b] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)** • **Dexamethasone** (when combination with remdesivir cannot be used or is not available) **(BI)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone (AI)** • **Dexamethasone plus remdesivir**[b] **(BIII)** For recently hospitalized[c] patients with rapidly increasing oxygen needs and systemic inflammation: • Add either **baricitinib (BIIa)** or **IV tocilizumab (BIIa)** to one of the two options above[d] • If neither baricitinib nor IV tocilizumab is available or feasible to use, **tofacitinib** can be used instead of baricitinib **(BIIa)** or **IV sarilumab** can be used instead of IV tocilizumab **(BIIa)**.
Hospitalized and Requires IMV or ECMO	• **Dexamethasone (AI)** For patients who are within 24 hours of admission to the ICU: • **Dexamethasone plus IV tocilizumab (BIIa)** • If IV tocilizumab is not available or not feasible to use, **IV sarilumab** can be used **(BIIa)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Figure 6b. NIH Recommendations for the prevention and prophylaxis of COVID-19.

Prevention and Prophylaxis of SARS-CoV-2 Infection

Last Updated: July 8, 2021

Summary Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends that health care providers follow recommendations from the Advisory Committee on Immunization Practices when using SARS-CoV-2 vaccines **(AI)**.
- The Panel **recommends against** the use of any drugs for SARS-CoV-2 pre-exposure prophylaxis (PrEP), except in a clinical trial **(AIII)**.
- The Panel **recommends against** the use of **hydroxychloroquine** for SARS-CoV-2 post-exposure prophylaxis (PEP) **(AI)**.
- The Panel **recommends against** the use of other drugs for SARS-CoV-2 PEP, except in a clinical trial **(AIII)**.

2. Pre and Postexposure Prophylaxis (The I-MASK+ protocol)

The components of the I-MASK Prophylaxis and Early Treatment protocol are illustrated in Figures 7a-c. Recent data suggests that ivermectin, melatonin as well as the combination of quercetin (or mixed flavonoids) and vitamin C may play an important role in both pre-exposure and postexposure prophylaxis. [2,9] The evidence supporting the use of Ivermectin for the prophylaxis of COVID-19 is provided by the comprehensive review by Kory et al. [10] It is important to emphasize that ALL of the medications included in our prophylactic regimen are inexpensive, safe, and widely available. The I-MASK + protocol MUST be part of an overall strategy which includes common sense public health measures, i.e., masks, social distancing, and avoidance of large groups of people.[11]

2.1 Core Components of the I-MASK Prophylactic Protocol

- Ivermectin for postexposure prophylaxis (see ClinTrials.gov NCT04422561). 0.4 mg/kg immediately then repeat 2nd dose in 48 hours. Ivermectin is best taken with a meal or just following a meal (greater absorption). [12] Oropharyngeal sanitation also suggested (see section on home treatment below).
- Ivermectin for pre-exposure prophylaxis (in HCW) and for prophylaxis in high-risk individuals (> 60 years with co-morbidities, morbid obesity, long term care facilities, etc). 0.2 mg/kg per dose - start treatment with one dose, 2nd dose 48 hours later, then 1 dose every 7 days (i.e. weekly).[13-18] For those at high risk of contracting COVID-19 we now recommend twice weekly dosing. See dosing Table below. Ivermectin has a number of potentially serious drug-drug interactions; please check for potential drug interactions at Ivermectin Drug Interactions - Drugs.com (also see below) . The most important drug-drug interactions occur with cyclosporin, tacrolimus, anti-retroviral drugs, and certain antifungal drugs. While ivermectin has a remarkable safety record, [19] fixed drug eruptions (diffuse rash) and Stevens Johnson Syndrome have rarely been reported. [20,21] While hepatitis is commonly quoted as a side effect, we are aware of one published case report of reversible hepatitis.[22] The safety of ivermectin in pregnancy has not been determined. [23] Ivermectin may increase the risk of congenital malformations particularly when used in the first trimester. [23] US Food and Drug Administration (FDA) has classified ivermectin as pregnancy category C—i.e, "Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks". In pregnant patients with symptomatic COVID-19 infections the risk and benefits of ivermectin should be discussed with the patient, and informed consent obtained from the patient should the drug be prescribed. Additionally, women should be counselled that low concentrations of ivermectin are present in breast milk; the implications of this finding are unclear.[24]
- Melatonin (slow release): Begin with 0.3 mg and increase as tolerated to 6 mg at night. [1,9,25-31]. Melatonin has anti-inflammatory, antioxidant, immunomodulating and metabolic effects that are likely important in the mitigation of COVID-19 disease.[32-34] A recent large retrospective study demonstrated that the use of melatonin in intubated patients with COVID-19 significantly reduced the risk of death (HR 0.1; p=0.0000000715).[33] It is intriguing to recognize that bats, the natural reservoir of coronavirus, have exceptionally high levels of melatonin, which may protect these animals from developing symptomatic disease. [35] The slow release (extended release) formulation of melatonin is preferred as it more closely replicates the normal circadian rhythm. [25] There is marked inter-individual variation in the metabolism of melatonin (first pass metabolism) hence the dose must be individualized.[25] High serum levels are associated with hyper-REM sleep and bad dreams. Rapid release melatonin (usual over the counter formulation) results in early high peaks that do not replicate the normal circadian pattern; hence it is important to take the slow release/extended-release formulation.