



COVID-19 Key Research Questions and Recommendations

Identifying and prioritizing key research questions is necessary for the rapid development of successful diagnostics, therapeutics, and public health interventions in the fight against COVID-19. The Infectious Diseases Society of America (IDSA) has compiled a comprehensive list of COVID-19 clinical trial and research recommendations for federal agencies and investigators below.

COVID-19 CLINICAL TRIAL RECOMMENDATIONS

- As multiple federal research agencies have demonstrated, it is most ethical and prudent to enroll patients with COVID-19 in clinical trials rather than use clinically unproven therapies. There are multiple ongoing trials, some with adaptive designs, which potentially can quickly answer pressing questions on efficacy and safety of drugs in the treatment of patients with COVID-19. Where lack of access to clinical trials exist, we encourage **setting up local or collaborative registries to systematically evaluate the efficacy and safety of drugs to contribute to the knowledge base**. During such a pandemic, barriers to conducting studies and enrolling patients in trials for already overburdened front line providers should be minimized while ensuring the rights and safety of patients.
- For clinical trials and observational studies, it is critical to determine *a priori* standardized and practical definitions of patient populations, clinical syndromes, disease severity, and outcomes.
- For clinical syndromes, **clearly distinguishing between asymptomatic carrier state, upper respiratory tract infection, and lower respiratory tract infection** is important. Illness severity should be reasonably defined using readily available clinical criteria of end organ failure (e.g., the degree of respiratory failure using SaO₂ or FiO₂:PaO₂ ratios for lower respiratory tract infection) as opposed to location-based severity determinations such as ICU admission, which can lead to bias based on resource limitations or regional/institutional practice patterns.
 - It is also critical to **develop a core set of definitions for upper and lower respiratory disease and definitions for disease severity**. The heterogeneity of the current research landscape will make it difficult to compare data across different studies.
- For outcomes of prophylaxis trials, the primary endpoint should be prevention of infection or illness. For therapeutic trials, measurable patient-centered outcomes include reduction of mortality; duration of symptomatic illness; and need and duration of hospital/ICU stay.
- Trials should also study **treatments in high risk populations or special populations like immunosuppressed patients, people with HIV, patients with cardiovascular comorbidities, pregnant women, and newborns**.

IMPLEMENTATION CONSIDERATIONS

- Clinical laboratories work with BSL2+ but are being asked to use BSL3 precautions for research. This limits the number of people who can perform laboratory research (i.e., isolate lymphocytes or nucleic acids to study viral evolution or host immune responses). Therefore, some research will only be possible in a limited number of laboratories and institutions with BSL3 availability or modified biosafety rules. **A common guideline for research should be developed that can be used by all institutions, while maintaining safety for laboratory staff**. Recommendations may need to be stratified based on the potential for safe handling of study materials.

- Determine which animal or other model(s) are most appropriate for studies and increase production and availability of those animals/systems.
- It is essential, but logistically difficult, to conduct studies in the outpatient setting. **Develop common guidelines for research in outpatient settings and establish networks through which outpatient settings can collaborate on COVID-19 research.**
- The infectious diseases scientific workforce must be expanded. **Increase compensation for pediatric and adult ID physician-scientists and the number of federal grants available to young investigators in ID to attract necessary new talent to the field.**
- **Develop a multi-stakeholder partnership to address data/specimen collection and protocols for storage and analysis.** Community trust and engagement with diverse populations is essential.
- **Coordinate between centers and researchers to enroll patients across the country into various studies.** Ideally this would occur via central IRB submissions with nationwide enrollment and quick buy-in by local IRBs and R&D committees
- **Public health infrastructure must be strengthened** to prepare facilities and systems to roll out vaccination and diagnostics at the population level.

RESEARCH RECOMMENDATIONS BY SUBJECT AREA

INFECTION PREVENTION

- Clinical studies are needed to inform our understanding of SARS-CoV-2 respiratory transmission in the healthcare setting. Studies are especially needed to clarify which medical procedures require a higher level of respiratory protection.
- Randomized controlled trials and prospective outcome registries are needed to inform strategies to prevent infection in HCP during contingency and crisis settings in which recommendations for use of PPE in conventional settings cannot be adhered to.
 - Characterize impact of extended use and re-use on N95 respirator fit and filtration, including identifying simple thresholds above which these strategies would no longer be recommended;
 - Techniques for safely storing the N95 respirator between reuse (e.g., in a clean, breathable container) and preventing HCP contamination during donning and doffing.

DIAGNOSTICS

- Well-designed studies are needed to compare the performance characteristics of the different assays that are available for adult and pediatric populations; comparing different specimen types (NP, nasal, OP, saliva, mid turbinate, stool) and comparing healthcare-collection to patient-collection of specimens in different populations
 - For ICU, ambulatory, and general ward patients, comparing upper and lower respiratory tract samples is critical.
 - Understand how test performance varies as a function of specimen type and time from symptom onset
- Quantitative platform (prognostication)
- Serology (time course for seroconversion; surveillance; vaccine development)
- Clinical decision support tools for testing (diagnostic stewardship)
- Funding for expansion of infrastructure for diagnostic testing
- Testing strategies including test accuracy for asymptomatic patients
- Determine the role and timing for retesting a positive patient and whether retesting impacts safe clinical care
- Test performance and identifying potential “gold standard” comparator
 - Define the clinical sensitivity and specificity of NAAT for the diagnosis of COVID-19 stratified by duration of symptoms and severity of disease

- Compare accuracy/yield of different specimen types
- Compare the accuracy of different EUA approved NAAT platforms

TREATMENT

- Antivirals
- Role of steroids and other anti-inflammatory agents
- Immunotherapeutics (e.g., Tocilizumab)
- Role of anticoagulation and antiplatelet therapy
- Post-exposure prophylaxis (in vulnerable populations)
- Drug safety, especially in patients with cardiovascular disease, immunosuppressive conditions, or those who are critically ill with multi-organ failure
- Repurposing of drugs like chloroquine or hydroxychloroquine
- Evaluate disparities in clinical outcomes
- Antibiotics for secondary bacterial infections
- Appropriateness of antibiotic use for COVID-19 patients and impact of antibiotic use on COVID-19 patients on antimicrobial resistance; antimicrobial stewardship and secondary infections
- Other interventions (e.g., convalescent plasma, zinc, Vitamin D)

EPIDEMIOLOGY

- Zoonotic transmission
- Viral evolution
- Transmission dynamics & contact tracing
- Prospective cohort studies (classifying symptomatic and asymptomatic ratios, risks)
- Follow-up studies to see long-term impacts in patients who survive. Whether immune parameters change? Other?
- Improved methods for international monitoring for the next zoonotic pathogen
- Longitudinal cohort studies of symptomatic and asymptomatic patients of all ages – what are the dynamics of the antibody response over time? Can we estimate time-since-infection from antibody response? Are there unanticipated long-term outcomes (e.g., accelerated cardiovascular disease, “sanctuary sites”, other)?
- Determining correlates of disease progression and identifying epidemiologic risk factors that contribute to increased adverse outcomes in specific minority populations
- Cross-sectional seroprevalence - what are the age-specific and spatial distributions of prior exposure?
- Household contact studies – what baseline serological responses correlate with protection? What are the risk factors for symptomatic infection?

PATHOGENESIS

- Children (e.g., kinetics & duration of viral shedding); identifying potential correlates of protection in children
- Risks of vertical transmission of SARS-CoV2 and the impact COVID19 has in the mother-infant dyad during pregnancy and postnatally in both mother and newborn.
- Adult groups (e.g., kinetics & duration of viral shedding in different populations such as immunocompromised persons, persons living with HIV, cystic fibrosis)
- Risk factors for severe disease; How does the risk profile (comorbidity) differ depending on age?
- Correlation or causation relationship between ACE2 receptor/ACE-inhibitors/ARBs/TMPRSS2 and disease severity
- Studies on seroconversion and whether/which antibodies confer immunity (or modified disease course with second infection)

- Pathogenesis of lung/ cardiac damage and whether therapeutics targeting damage (e.g., ill-6 inhibitor) would be beneficial
- Determine the significance of viral co-infections (especially with influenza) in clinical outcomes.
- Biobanking of samples - should include respiratory, serum, and stool at minimum. If these could be sampled longitudinally they could be followed to see differences between those who convalesce and those who do not survive.
- How the lung microbiome modulates the response to COVID-19 in terms of severity and outcomes, given that there is [evidence](#) supporting its importance. For operationalizing such insights, can also prioritize studies utilizing rapid sequencing and bioinformatics pipelines with turnaround time measured in hours, like those enabled by metagenomics on, for example, the MinION sequencing platform.

VACCINOLOGY

- Pre-clinical to clinical jump
- Phase 1-3 to licensure
- Studies on passive immunization with monoclonal antibodies (mAb) to viral antigens
- Identify correlates of protection to COVID-19; exploring these areas may be key to development of effective vaccines and immunotherapies.
- Assays to differentiate vaccine-induced immune response from natural COVID-19 immunity
- Strategy for prioritizing targets for initial vaccination based on risk and epidemiology data