TOWARD A COMPREHENSIVE AND COORDINATED COVID-19 RESEARCH AGENDA
Toward a Comprehensive and Coordinated
COVID-19 Research Agenda

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The COVID-19 Research Working Group

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EXECUTIVE SUMMARY

SARS-CoV-2 is not the first novel coronavirus to cause a widespread threat to global health, and it is unlikely to be the last. In order to better understand COVID-19 and other coronaviruses and develop effective prevention and treatment modalities, a comprehensive strategy is needed to guide research, vaccine, and drug development programs within the US and around the world. Despite significant investment and progress in vaccine development and the recent approval of the first COVID-19 vaccines, overall research efforts by the US will benefit from a more detailed strategy and higher-level interagency coordination.

This document highlights priority areas to be addressed as part of a comprehensive COVID-19 research agenda. It is prepared by the COVID-19 Research Working Group—an ad hoc group of health advocates, researchers and providers. Rather than covering all areas of research, the document focuses on issues across the spectrum from basic biomedical to implementation research that, so far, have not been addressed sufficiently.

We present this document to the NIH, other federal agencies responsible for research and implementation, other funders, and COVID-19 stakeholders, as a starting point for discussion and further analysis of the current research portfolio, as well as for examining how COVID-19 research is prioritized, guided and coordinated within and between US government agencies, academic research centers, public health agencies, and the pharmaceutical industry. We fully recognize that SARS-CoV-2/COVID-19 is an emergent and novel virus, and that both science and practice related to it are constantly evolving. What we present below is a snapshot at one point in time, but we believe that the core questions and concerns we raise will remain relevant and applicable to the research response going forward—not just in relation to COVID-19, but for future pandemic threats as well.

To ensure robust facilitation and coordination of all aspects of pandemic response—from discovery research to public health implementation—a dedicated office within the federal government is necessary. It is late in the day to achieve optimal coordination for addressing COVID-19, but there still is much that such an office can do to mitigate further chaos. Going forward, this office must focus on preparedness, so that once the next pandemic arrives, it will not be too late to respond effectively.

Immediately below are the recommendations contained within this report. The full discussion through which these recommendations were developed follows.
Transmission and immune response:
1. NIH, in coordination with other funders, should support, and oversee studies—from materials science and virology to epidemiology and modeling—on the dose of SARS-CoV-2 needed to cause COVID-19, the possible routes of transmission, the most common routes of transmission, and the effectiveness of non-pharmaceutical interventions to disrupt transmission, including mask wearing, meeting outside, and distancing.

2. NIH should support and oversee high quality prospective cohort studies on both COVID-19-negative and COVID-19-positive individuals.
   - These studies should evaluate the array of COVID-19 symptomology in diverse populations.
   - Separate studies should evaluate the immune response over time, both the humoral and the T-cell and B-cell response.
   - Cohort studies should also enroll individuals who have received authorized vaccine candidates to measure efficacy in preventing asymptomatic infection, as well as provide insights into the differential immunological responses between vaccinated individuals and those who have acquired immunity through natural infection.

Diagnostics:
1. NIH, in coordination with the FDA and the Biomedical Advanced Research and Development Authority (BARDA), should evaluate and implement a national testing agenda to ensure high quality, rapid, and low-cost testing nationwide, including:
   - Guidelines with different algorithms to inform how to use tests informed by variations in caseload, laboratory infrastructure, and disease prevalence across states/localities.
   - An evaluation and a comparison of locations/systems that have successfully used testing in this way (e.g. the NBA, college campuses, and nations).
   - A systematic meta-analysis of all available data on testing and the reproduction rate of COVID-19.

2. NIH should assemble and make widely available a COVID-19 sample repository with well-defined and validated characteristics to assist in the development and evaluation of COVID-19 diagnostic and serological tests.

3. NIH should initiate quality control and implementation studies to determine which SARS-CoV-2 diagnostic and serological tests should be recommended in terms of specificity and sensitivity, cost, accessibility, scalability, and ease of use from both the individual and public health perspective.

4. The federal government must coordinate with the private sector to develop rapid, easy-to-use SARS-CoV-2 diagnostic and serological point of care and home-based tests.
Therapeutics:
1. NIH should develop an integrated plan, including public and private partnerships, that aims to develop small molecule therapeutics. NIH and other funders should fund large, adaptive trials for COVID-19 therapeutics, including those that allow for adding or removing arms. Promising therapeutics should be immediately included onto these pre-existing trials.
2. NIH and other funders should ensure that studies of similar therapies, such as different monoclonal antibodies, are compared head-to-head in the initial clinical trials (to aid in implementation).
3. NIH and other funders should ensure that clinical trial protocols are centrally coordinated to promote comparison between the findings from various trials.
4. NIH and other funders should ensure that clinical trial recruitment focuses on diverse patient populations with attention to demographic characteristics and disease-stage.

Behavioral and Social Science:
1. NIH should support rapid research on how individuals, social networks, and communities devise decision rules for how they engage with others during COVID-19. Relevant questions include:
   • What kinds of algorithms, based on what inputs from which sources do people construct for making behavioral decisions, such as wearing masks, limiting social interactions, quarantining, traveling, testing, etc.?
   • How is this done in a context of uncertainty, as information (both scientific and policy-related) is constantly evolving and changing?
   • Are there extant, user-friendly, decision tools (e.g., from other infectious disease outbreaks) that can be modified and used for COVID-19 to understand uptake of non-pharmaceutical and testing interventions?
2. NIH should support rapid research on from where and from whom people get clues about what to do in response to COVID-19 and how this becomes internalized to affect behaviors. Relevant questions include:
   • How do people balance conflicting norms/identity-based values?
   • What is the role of social media?
   • What are the most productive ways to frame public health messages in different communities that can be delivered by trusted leaders?
3. NIH and other funders should support research to identify best practices for balancing acknowledgment and respect for the lived experiences and shared concerns of communities with evidence-based public health information to facilitate health-promoting practices among these communities.
4. NIH and other funders should support robust health communications research to determine what tools exist to mitigate vaccine hesitancy and promote vaccine confidence that can be adapted for COVID-19, and to identify efficacious strategies for combating and debunking health-related conspiracy theories and misinformation in light of the impact of social media.

5. NIH and other funders should rapidly support the development of a national behavioral monitoring tool to gather insights about what is driving behavioral change in response to COVID-19 over time. This could be a periodic, cross-sectional survey to allow for rapid and adaptive monitoring of core variables related to demographics, preventive behaviors, knowledge, risk perception, trust, and stigma.

**Implementation Science:**

1. NIH should work with its HHS partner agencies to develop a coordinated COVID-19 implementation science research agenda with specific funding. This agenda should include:
   - Research on how best to respond to COVID-19 after vaccines become available.
   - Research on care delivery approaches using adaptive study designs that can change with the introduction of new technologies and research outcomes.
   - Investigation of the value of utilizing community systems for information dissemination, support services, testing and vaccine administration.

2. The US Government must invest in planning for a coordinated scale-up of manufacturing capabilities for mAbs to ensure that if an antibody is found to be safe and effective, it could be made available to all who need it in an expeditious manner.

3. NIH and other funders should support implementation science on how best to prepare for the next pandemic.

**Community Engagement:**

1. NIH should ensure that two civil society representatives are members of the ACTIV and COVPN convening group.

2. NIH and NIAID should add three civil society representatives within each of the ACTIV workgroups.

3. NIH should commit to having at least two members representing civil society on each study protocol for all COVID-19 research areas.

4. NIH should ensure that all COVID-19 prevention and treatment research study sites have Community Advisory Boards that reflect the epidemic.

5. NIH and other funders should provide support and capacity-building to community representatives participating in COVID-19 research development and implementation.
INTRODUCTION

Since SARS-CoV-2/COVID-19 emerged in late 2019 over 75 million cases of COVID-19 and over 1.6 million related deaths have been reported globally. The United States (US) continues to bear the greatest burden, with over 17 million cases and over 300,000 deaths at the time of this writing. While rates of new COVID-19 cases and deaths have fluctuated during the year, both currently are growing at an alarming pace throughout the world, including the US, and are expected to continue through early 2021.

There is some light at the middle, if not the end, of the tunnel, as we now have encouraging preliminary results from two large COVID-19 mRNA vaccine trials—sponsored by Pfizer/BioNTech and Moderna—that each have shown efficacy of over 90%. A third trial, conducted by AstraZeneca and Oxford University using a viral vector vaccine appears to be somewhere between 62% and 90% effective, depending on dosage, although some concerns have been raised about the meaning and validity of the data. While finalizing this document, both the Pfizer vaccine and the Moderna vaccine were authorized for use in the United States. The prospect of a highly effective vaccine for COVID-19 would drastically change the landscape of the pandemic; however, the results remain preliminary and it is not currently clear the length of protection the vaccines may offer. Further, while millions of doses of the Pfizer and Moderna vaccine will be available by January 2021, our nation alone would need hundreds of millions of doses to achieve herd immunity. This, quite simply, will take time and the overcoming of huge logistical challenges in the production and distribution of the vaccines. Issues with public trust and vaccine uptake may also slow this process. Lastly, for the foreseeable future and until high global coverage is achieved with an efficacious vaccine, other protective public health measures will need to remain in place.

Thus, while these and potentially other vaccines are being pursued, diagnostics and treatment of COVID-19 must continue to be emphasized. This work will help us in controlling further transmission of SARS-CoV-2, diagnosing of cases and treating people effectively. Such progress will also help prepare us for the possibility of another coronavirus pandemic or a pandemic caused by other pathogens in the future.
The federal research response to COVID-19 has thus far invested significantly more resources in vaccine research and development than research related to diagnostics, treatment (Figure 1) or non-pharmaceutical prevention. This despite the fact that COVID-19 treatments, diagnostics, and non-pharmaceutical prevention will be necessary for years to come even as vaccines are rapidly developed.

Testing for COVID-19 remains complex and shows little evidence of a nationally-coordinated approach, with turnaround times for test results lagging in some regions, poor sensitivity of rapid tests, and a lack of inexpensive, home-based, rapid, accurate testing that could be transformative in efforts to prevent transmission of the virus. Understanding remains limited about the immune response to SARS-CoV-2 infection, the trajectory of the disease course—including the risk for long-term symptoms, the ways in which the disease affects different populations, and the factors that affect the severity of illness. While improvements have been noted in patient outcomes as health care providers have gained experience in managing COVID-19, there still are few safe and effective treatments for COVID-19. In addition, many questions remain about the factors associated with adoption of and sustained adherence to behavioral preventive interventions, and how inequities and disparities by race, class, gender, and geography affect such factors. Similar questions are relevant to vaccine acceptance and coverage.

SARS-CoV-2 is not the first novel coronavirus to cause a widespread threat to global health, and it is unlikely to be the last. In order to better understand COVID-19 and other coronaviruses and develop effective prevention and treatment modalities, a comprehensive strategy is needed to guide research, vaccine, and drug development programs within the US and around the world. Despite significant investment in vaccine development, the overall SARS-CoV-2/COVID-19 research effort remains disjointed and poorly articulated.

The National Institutes of Health (NIH) has developed an NIH-Wide Strategic Plan for COVID-19 Research that outlines a framework for its research funding, organized around five strategic priorities: 1) improve fundamental knowledge; 2) advance research to improve detection; 3) support research to advance treatment; 4) accelerate research to improve prevention; and 5) prevent and redress poor COVID-19 outcomes. Within each of these priorities, a number of very broad approaches are noted. While this is a good beginning with respect to articulating a coherent trans-NIH COVID-19 research agenda, at this
stage the Plan lacks the level of specificity and transparency about coordination that is needed to
guide and focus the research response, including the level of investment to be allocated to each
strategy as well as how the strategy will drive the research funding priorities. Moreover, a number of
important research areas are missing from this Plan.

Our document highlights priority areas that must be addressed as part of a comprehensive COVID-19
research agenda. It is prepared by the COVID-19 Research Working Group—an ad hoc group of
health advocates, researchers, and providers. Rather than covering all areas of research, the
document focuses on issues across the spectrum from basic biomedical to implementation research
that, so far, have not been addressed sufficiently. (For example, because they have received a great
deal of attention elsewhere, basic research on viral pathogenesis and on infectious disease modeling
are not emphasized here.) Throughout the document, we raise a number of important questions, such
as:

• What are the most efficient means of transmission of SARS-CoV-2? To what degree does risk
  vary by exposure?
• What are the factors that determine whether infection is asymptomatic, symptomatic or severe?
• What is the prevalence of long-term sequelae? What are the risk factors and pathogenetic
  mechanisms of long-term sequelae? And what is the trajectory and prognosis for individuals
  with such sequelae?
• How do symptoms differ by age, race, gender, and health status?
• How have death rates changed since the beginning of the pandemic and why?
• Are antibodies protective, which types of antibodies are protective, at what threshold and
  how durable are such antibodies?
• What is the role of cell-mediated immune response in protection against SARS-CoV-2 infection?
• How prevalent is reinfection and what determines risk for reinfection?
• How effective are various behavioral interventions (e.g. physical distancing, face-covering/
  masking) at preventing SARS-CoV-2 transmission and how can their adoption and adherence
  be enhanced?
• How efficacious are various structural interventions (e.g. school closure, movement
  restrictions) to prevent SARS-CoV-2 transmission and how can their adoption and adherence
  be enhanced?
• How can access to rapid, easy-to-use, inexpensive, and accurate home-based testing become
  a reality?
• What would be the most effective and efficient testing regimen with a home-based test?
• How can a frequent rapid test regimen be deployed to re-open society and the economy?
• How can individuals accurately assess their own risks of acquiring or transmitting SARS-CoV-2?
• What are effective interventions to enhance uptake of vaccines in order to achieve high coverage?
• What are effective strategies for engaging communities and trusted leaders within them to enhance uptake of diagnostic, prevention, and treatment strategies?
• What are effective strategies for addressing racial and social inequalities as these are manifest in COVID-19 and other health disparities?

We present this document to the NIH, other federal agencies responsible for research and implementation, other funders, and COVID-19 stakeholders, as a starting point for discussion and further analysis of the current research portfolio, as well as for examining how COVID-19 research is prioritized, guided, and coordinated within and between US government agencies, academic research centers, public health agencies, and the pharmaceutical industry. We fully recognize that SARS-CoV-2/COVID-19 is an emergent and novel virus, and that both science and practice related to it are constantly evolving. What we present below is a snapshot at one point in time, but we believe that the core questions and concerns we raise will remain relevant and applicable to the research response going forward—not just in relation to COVID-19, but for future pandemic threats as well.

1. TRANSMISSION, TRAJECTORY, AND IMMUNE RESPONSE

SARS-CoV-2 initially was noted as a cause of acute respiratory illness and an unexplained pneumonia, but further research revealed that 80% of individuals infected with the virus have mild or moderate illness that does not require hospitalization, with a substantial proportion of individuals who never develop symptoms. Therefore, by the time a significant number of severely ill COVID-19 patients are admitted to a hospital, it is likely that community spread has been ongoing with asymptomatic and/or mildly symptomatic cases occurring undetected in a population.

SARS-CoV-2 was initially thought to transmit mainly through large respiratory droplets and short-lived fomites, essentially droplets that have landed on a surface. There is significant controversy regarding the role of aerosols in SARS-CoV-2 transmission; while there is experimental evidence to support stability of the virus in aerosols and on surfaces, there is little data to inform the role and magnitude of such routes in transmission in the human population.
Research in animal models, combined with computational biology, epidemiology, and modeling studies, must address these fundamental questions in viral transmission. Studies should be prioritized to focus on questions such as the minimum dose of infectious virus required for COVID-19 disease, whether the dose of virus with which one is infected determines the severity of COVID-19 disease, and what routes (droplet, aerosol, fomite, fecal-oral) can occur and which routes drive most transmission at the population level. Epidemiological studies should focus specifically on different physical sites of transmission, including schools, workplaces, public transportation, bathrooms, and homes. The degree to which mask wearing affects the risk of an individual, or others around that individual, to either transmit or acquire infection should be assessed in further detail using studies in fields from materials science and virology to population epidemiology.

In early research on the initial outbreak in Wuhan, China, researchers showed that the most common symptoms of acute SARS-CoV-2 infection (also known as COVID-19) largely target the lungs with symptoms including fever, fatigue, cough, and shortness of breath. Since these early studies, additional symptoms have been identified and evidence of involvement of other organ systems has been noted, including thrombotic events, neurological symptoms including loss of taste and/or smell, cardiovascular damage, and severe immune system dysregulation. Many of these symptoms, in their most severe states, can lead to severe sequelae including lung damage, heart damage, acute respiratory distress syndrome, renal failure and immune overactivation (also known as a ‘cytokine storm’), leading to death in a substantial proportion of those with severe disease.

**SYSTEMATIC UNDERSTANDING OF COVID-19 CLINICAL COURSE**

To date, studies to estimate the proportion of COVID-19 cases that are asymptomatic, mildly symptomatic, moderate, and severe, largely based on early experience in China, have provided somewhat inconsistent results, likely due to the difficulty in defining truly asymptomatic and mild but subclinical cases (with fatigue, for example, being the most common symptom of COVID-19 reported in some studies).

Large prospective cohort studies are needed to address fundamental questions about the course of SARS-CoV-2 infection, the organ systems most commonly affected, the range of symptoms, and the long-term effects in diverse populations (in relation to, e.g., age, sex, comorbidity, geography, clinical intervention, etc.).
Diverse cohorts can address specific questions. For example, a cohort of SARS-CoV-2 naïve individuals at high risk for infection (e.g., health care workers or essential employees), recruited from areas with high transmission rates, tested frequently for viral RNA and COVID-19 symptoms, will be essential to address the question regarding the exact proportion of individuals who show no or mild symptoms. Large long-term, longitudinal cohort studies will allow the study of both rates of infection in populations and the determination of the long-term effects of SARS-CoV-2 infection (for example what proportion of cases develop long term symptoms/sequelae). Similarly, longitudinal studies of patients with COVID-19 are needed to address the duration of viral shedding (currently estimated at two weeks in relatively small studies), the duration of symptoms, the type and duration of immune response (including antibodies, memory B-cells, and T-cells), and the long-term consequence of infection. Such cohort studies could also inform questions such as risk of transmission within households and beyond as well determinants of such transmission. It is critical to ensure that participants who become vaccinated remain in the cohort to be followed longitudinally in order to accrue knowledge about the ways in which vaccination with different products may affect patterns of symptoms and immune responses.

**COVID-19 IMMUNE RESPONSE**

Upon infection with a pathogen, the host typically mounts a robust immune response that includes both the innate and adaptive immune systems. Within a week of infection, the adaptive immune system typically responds providing in some (but not all) situations lasting immunity against reinfection, with an antibody response mediated by B-cells and a cellular response that is T-cell mediated, though there are exceptions to this. Such antibodies, known as neutralizing antibodies, can bind to and inactivate the pathogen upon reinfection. The level and duration of each of these adaptive components of the immune system is highly variable and must be studied in large populations for each pathogen.

Small studies, with around a dozen acute COVID-19 patients, have evaluated the T-cell and innate immune response to SARS-CoV-2. Larger studies with up to 30,000 individuals provide information on SARS-CoV-2 specific antibodies after infection and are ongoing. Results are still mixed on magnitude of total antibody versus neutralizing antibody response, the relationship between antibody levels and the ability of these antibodies to neutralize the virus and the duration of high antibody titer as well as their protective effect. Multiple cohort clinical trials are currently planned or recruiting to help us better understand both cell-mediated and antibody immunity in patients who have been infected with SARS-CoV-2. Federally funded cohort studies investigating the immune response to SARS-CoV-2 include the following:
<table>
<thead>
<tr>
<th>NCT</th>
<th>Title</th>
<th>B-Cell or T-Cell</th>
<th>Follow-up</th>
<th>Study Size</th>
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<tr>
<td>NCT04362865</td>
<td>Investigation of the B- and T-cell Repertoire and Immune Response in Patients With Acute and Resolved COVID-19 Infection</td>
<td>Both</td>
<td>2 years post infection</td>
<td>180</td>
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<tr>
<td>NCT04411147</td>
<td>A Longitudinal Study of COVID-19 Sequelae and Immunity</td>
<td>Both</td>
<td>3 years post infection</td>
<td>900</td>
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<tr>
<td>NCT04403386</td>
<td>Prospective Natural History Study of Smoking, Immune Cell Profiles, Epigenetics and COVID-19</td>
<td>CD16+CD8+ T cells</td>
<td>Pre/Post Infection</td>
<td>200</td>
</tr>
<tr>
<td>NCT04582903</td>
<td>Send-In Sample Collection for Comprehensive Analyses of Innate and Adaptive Immune Responses During Acute COVID-19 and Convalescence</td>
<td>Unclear, likely cytokine markers and antibodies, not sure if intact PBMCs for T cell analysis will be able to be recovered</td>
<td>At least once, in both confirmed infected patients as well as patient who have remained uninfected despite prolonged high risk exposure</td>
<td>500</td>
</tr>
<tr>
<td>NCT04378777</td>
<td>Immunophenotyping Assessment in a COVID-19 Cohort (IMPACC)</td>
<td>Antibody typing, kinetics, and functionality mid-infection, cytokine profiling</td>
<td>During hospitalization, q3 months for 1 year</td>
<td>2,000</td>
</tr>
<tr>
<td>NCT04565067</td>
<td>Identification and Characterization of SARS-CoV-2 Specific CD8 T Cells in Humans</td>
<td>CD8+ T-cells</td>
<td>recovered patients</td>
<td>120</td>
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<tr>
<td>NCT04431414</td>
<td>A Study of Immune Responses to the Virus That Causes COVID-19 (CoVPN 5001)</td>
<td>CD4+/CD8+ T-cells / B-Cells / Antibodies / cytokine profiling</td>
<td>Samples taken post 28 days infection</td>
<td>800</td>
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<tr>
<td>NCT04403880</td>
<td>Characterizing SARS-CoV-2-specific Immunity in Individuals Who Have Recovered From COVID-19</td>
<td>CD4+/CD8+ T-cells / B-Cells / Antibodies / cytokine profiling</td>
<td>1-8 weeks post resolution of COVID-19 OR 2-10 weeks post most recent positive SARS-CoV-2 test</td>
<td>727</td>
</tr>
</tbody>
</table>

Better understanding the immune response to COVID-19 and how it may protect individuals from
reinfection or the development of severe disease could help us better deploy vaccines and develop therapies. While multiple vaccine studies are underway, some of which have now released results, the relative ability of each vaccine candidate to prevent infection – i.e. provide “sterilizing” immunity – versus preventing severe or symptomatic disease is not yet understood. The Phase 3 clinical trials of the two mRNA vaccines from Pfizer/BioNTech and Moderna that have been approved by the FDA for Emergency Use Authorization were designed primarily to measure the efficacy in preventing symptomatic disease, not infection. At this point, limited data on the Astra Zeneca/Oxford adenoviral vector-based vaccine candidate has been released to adequately assess its ability to prevent either symptomatic or asymptomatic infection.

Given the authorization of at least two vaccine candidates to date, it is important that cohort trials be rapidly launched following vaccine approval to ascertain the ability of that vaccine to prevent asymptomatic infection. Ideally, such a cohort would be paired with unvaccinated individuals who have recovered from SARS-CoV-2 infection. This could allow researchers to ascertain if vaccine or naturally acquired immunity is protective against asymptomatic infection, and if so, the immunological determinants that provide such protection.

COVID-19, CO-MORBIDITIES, AND LONG-TERM SEQUALAE

Data to be collected from cohorts should be maximized to include sociodemographic, epidemiological, psychosocial and clinical characteristics and should aim to collect specimens for measurement of various biomarkers.

The cohort studies will help identify the specific risk factors for COVID-19 and complications among individuals, including those with comorbidities—such as HIV, cancer, neurodegenerative diseases, and Myalgic Encephalomyelitis (ME). This will help determine which patients may be at increased risk both of severe acute illness and long-term post-acute COVID-19 sequelae.

In addition to the population cohorts described above, patient cohorts should also be identified to enable the study of the likelihood and symptoms of post-acute COVID-19 disease. Currently, these patients are largely being treated due to their individual symptoms (e.g. lung damage, neurological symptoms, or post-viral fatigue). Cohorts of all post-acute COVID-19 patients may be useful in identifying molecular signatures of viral infection associated with long-term immune dysregulation and disease. Large cohorts of specific clusters of symptoms (for example neurological symptoms and post-viral fatigue and/or ME) are necessary to understand the disease progression. These studies could provide the framework and underlying work necessary to evaluate disease-specific interventions and therapeutics.
RECOMMENDATIONS:

1. NIH, in coordination with other funders, should support, and oversee studies—from materials science and virology to epidemiology and modeling—on the dose of SARS-CoV-2 needed to cause COVID-19, the possible routes of transmission, the most common routes of transmission, and the effectiveness of non-pharmaceutical interventions to disrupt transmission, including mask wearing, meeting outside, and distancing.

2. NIH should support and oversee high quality prospective cohort studies on both COVID-19-negative and COVID-19-positive individuals.
   - These studies should evaluate the array of COVID-19 symptomology in diverse populations.
   - Separate studies should evaluate the immune response over time, both the humoral and the T-cell and B-cell response.
   - Cohort studies should also enroll individuals who have received authorized vaccine candidates to measure efficacy in preventing asymptomatic infection, as well as provide insights into the differential immunological responses between vaccinated individuals and those who have acquired immunity through natural infection.
2. DIAGNOSTICS

Within weeks of the initial discovery of SARS-CoV-2 as the cause of severe pneumonia in Wuhan, China, scientists sequenced the viral genome. The virus was noted to be closely related to the coronaviruses that caused the previous SARS and MERS outbreaks. The sequence of the virus allowed scientists to rapidly develop genetic (RNA-based) tests for diagnosis of COVID-19: If the viral RNA fragments could be detected by qRT-PCR (a method used to amplify RNA), a person would be diagnosed with COVID-19. Subsequent laboratory diagnostic and serologic tools include tests for the individual’s antibody response to viral infection and rapid tools both for diagnosis (RNA or viral protein/antigen) or antibody detection. Most rapid tests use lateral flow assays to detect viral antigen or antibody, however, point of care tests to directly measure viral RNA are now commercially available under an Emergency Use Authorization (EUA) from the FDA.

Highly sensitive and specific, easy-to-administer, inexpensive, home-based rapid testing would provide the public with improved options to make decisions about how to engage with others, providing improved safety in schools, workplaces, homes, and other settings. It will be imperative to pair the deployment of such tests with clear messaging, either through a paired mobile app or broader public health messaging, about how results of such tests should be understood and their implication on behavior.

AVAILABILITY OF HIGH-QUALITY LABORATORY BASED ACUTE COVID-19 TESTING

The molecular biology of qRT-PCR-based COVID-19 testing is well established, but the US has had mixed success at implementing these tests for improved public health. Early in the COVID-19 crisis in the US, tests were severely limited to only those that could be sent to and performed at the CDC. After the FDA moved to approving commercial and laboratory-developed PCR tests for COVID-19 under EUAs, the availability of testing improved significantly. However, delays are still being reported due to a variety of issues, including cost, laboratory staffing, reagent and material availability, healthcare staffing to collect samples, and testing scale-up.

POINT OF CARE COVID-19 TESTING: NIH VALIDATION AND DEFINING OPTIMAL TESTING STRATEGY

The development and validation of rapid, point of care tests with high specificity and sensitivity will be an essential component of the response to COVID-19 in the coming months. Similar efforts are needed to validate rapid point of care antigen and antibody tests.
Antigen tests detect viral proteins (antigens) directly. These tests use lateral flow assay strips, similar to those used in at-home pregnancy tests, to identify viral proteins by binding them to antibody-conjugated lines on the test strip. Some point of care tests to amplify and identify viral RNA are currently in use and others are at various stages of product development. These tests use various methods of RNA amplification and detection, most typically LAMP to amplify RNA and then a color based or CRISPR/Cas9 based method to detect RNA. The manufacturers’ data show lower sensitivity than the laboratory-based RNA detection assays, but a high specificity.

Because the FDA only requires the manufacturer’s data for EUA authorization, external validation of COVID-19 tests already being used on patient samples has come largely from work by independent, academic researchers. The NIH should immediately undertake a quality control study evaluating all the currently available COVID-19 point of care tests against a large gold standard set of patient samples. Determining test sensitivity and specificity will be critical for their immediate use in clinical settings for diagnosis and at large scale for city-wide (or campus, care facility, etc.) COVID-19 surveillance.

A complementary study should focus on the best testing strategy for achieving optimal public health outcomes. Modeling studies indicate that frequency of screening and speed of reporting results are more critical than sensitivity of a specific assay. Such studies note that an easy to use, cheap screening assay with 70% sensitivity deployed every two days was the most effective testing strategy for case detection and containment of outbreaks. These modeling studies need to be validated by research on various approaches and their success at mitigating COVID-19 transmission. Real world studies to compare sensitivity and cost effectiveness of frequent testing regimens to a PCR-based gold standard would be valuable in order to understand the ways in which such testing regimens could be deployed to facilitate safe reopening of society and the economy.

The NIH should coordinate the results of these studies (and pre-existing data) with the CDC to release clear and concise testing guidelines for various settings (e.g., universities, schools, businesses), including which tests to use, how to interpret the results, and when to implement additional non-pharmaceutical interventions to limit the spread of a COVID-19 cluster.
.RECOMMENDATIONS:

1. NIH, in coordination with the FDA and the Biomedical Advanced Research and Development Authority (BARDA), should evaluate and implement a national testing agenda to ensure high quality, rapid, and low-cost testing nationwide, including:
   • Guidelines with different algorithms to inform how to use tests informed by variations in caseload, laboratory infrastructure, and disease prevalence across states/localities.
   • An evaluation and a comparison of locations/systems that have successfully used testing in this way (e.g. the NBA, college campuses, and nations).
   • A systematic meta-analysis of all available data on testing and the reproduction rate of COVID-19.

2. NIH should assemble and make widely available a COVID-19 sample repository with well-defined and validated characteristics to assist in the development and evaluation of COVID-19 diagnostic and serological tests.

3. NIH should initiate quality control and implementation studies to determine which SARS-CoV-2 diagnostic and serological tests should be recommended in terms of specificity and sensitivity, cost, accessibility, scalability, and ease of use from both the individual and public health perspective.

4. The federal government must coordinate with the private sector to develop rapid, easy-to-use SARS-CoV-2 diagnostic and serological point of care and home-based tests.
3. THERAPEUTICS

Since the beginning of the pandemic, much of the world’s research and development efforts have been focused on developing vaccines to prevent COVID-19. As of this writing, two vaccines, developed by Moderna and Pfizer and BioNTech, appear to be efficacious in preventing symptomatic disease from SARS-CoV-2. As we were finalizing this report, the Pfizer vaccine and Moderna vaccine were authorized for use by the FDA. Another 16 vaccine candidates are in Phase 3 trials, and an additional 45 are in Phase 1 or Phase 2 trials. While this likely represents a seminal moment in the world’s response to the pandemic, it does not obviate the need for the development of effective therapies to treat SARS-CoV-2 and its sequelae.

Part of this need stems from what is not yet understood about the current vaccines. Most fundamentally, it is not yet known how effective they are at preventing transmission of SARS-CoV-2, versus preventing symptom development and severity, which is their primary study endpoint. Additionally, we do not yet know the durability of the vaccine efficacy.

If these vaccines are not effective in preventing transmission, individuals who are not or cannot be vaccinated will require other treatments to reduce the morbidity and mortality of SARS-CoV-2 infection. Even if these vaccines prove to be effective at stemming transmission (as many surmise they will be), therapeutic treatments likely will still be needed for some time. Despite vaccines currently being available to prevent twenty-seven different infectious diseases, the world has succeeded in eradicating only a single pathogen, smallpox, from human populations. Historically, diseases that are vaccine preventable are a significant driver of morbidity and mortality even decades after the introduction of a vaccine. For example, measles still kills over a one hundred thousand people a year, despite the development of a highly effective vaccine in 1963.

Unfortunately, so far, only a single effective class of therapies – glucocorticoids, such as dexamethasone and prednisone – have been demonstrated to reduce mortality in certain COVID-19 patients. Remdesivir, a small molecule antiviral drug developed through a collaboration between Gilead Sciences, Inc. and the US Government, has been shown to decrease recovery time, improve mortality rates for those receiving supplementary oxygen, and prevent progression to more severe respiratory disease, again chiefly among those receiving supplementary oxygen. Subsequent studies by the WHO showed no benefit even to these patients. In sum, remdesivir may offer some benefits to some patients, but on its own, it is not a sufficient treatment for most. Finally, convalescent plasma therapy, using blood from people who have recovered from COVID-19, has been given to some people who are hospitalized with
COVID-19. Data from small clinical trials and a national access program suggest that convalescent plasma may lessen the severity or shorten the duration of the disease. However, more research is needed to determine if convalescent plasma therapy will be an effective treatment option.

Following is a brief review of some core areas in COVID-19 treatment research—related to each phase of research development and to different classes of therapies—that to date have been underexplored and that require further attention and support.

**PRE-CLINICAL RESEARCH**

**Basic Science**

Pre-clinical research refers to the phase of drug development that occurs before human studies. SARS-CoV-2 is a novel pathogen, first discovered in late 2019, and thus much of its basic science, including its virology, remains poorly characterized. Given the emergence of three novel coronaviruses of significantly public health concern in the last 20 years, including SARS-CoV-1, MERS, and SARS-CoV-2, research on coronavirus virology likely will be beneficial even beyond this pandemic—better understanding coronavirus virology not only will save lives now, it also will prepare us to save lives in the future.

A priority area in SARS-CoV-2 basic science is “small molecules,” which refers to compounds that have a low molecular weight. In pharmacology, small molecule therapeutics are generally contrasted to biological macromolecules, like antibody-based therapies, that are produced in genetically engineered living cells versus synthetic chemistry. Generally, small molecules are easier to produce than biological macromolecule-based drugs.

**High Throughput Screening**

Another important aspect of preclinical research is the screening of molecules to determine whether they have biological activity against SARS-CoV-2. This process is known as high throughput screening and involves the evaluation of countless molecules to test for antiviral activity in test tube models, known as cell culture, of coronavirus infection. Molecules which show the ability to slow or stop viral replication in test tube models can be selected for further evaluation in animal model systems, and in clinical trials.

Studying SARS-CoV-2, like SARS and MERS, in cell culture requires specialized laboratories that are able to operate at biosafety level 3 (BSL-3), the second to highest level of biocontainment. The limited number and capacity of BSL-3 labs are critical barriers for research and development for small molecule-based therapeutics.
The NIH’s main high throughput screening center at the National Center for Advancing Translational Science (NCATS) operates as a BSL-2, precluding the screening of compounds with "wild-type" SARS-CoV-2. As a result, wild type virus screening occurs at contract research organizations (CROs) and smaller BSL-3 facilities across the nation, which has resulted in most molecules being only evaluated in a single cell line – Vero/E6 cells – for anti-wild type SARS-CoV-2 activity.

The failure to screen compounds in multiple cell lines may have led to the decision to put forth chloroquine and its prodrug, hydroxychloroquine, as possibly effective drugs for the prevention and treatment of COVID-19 in the spring of 2020. Initial screening in Vero/E6 cells showed a potent antiviral effect for chloroquine, but later evaluation in multiple other cell lines showed no similar effect. The illusory antiviral effect, which was the main basis of the promotion of this therapy, turned out to be due to a specific mechanism present only in Vero cells, and no other cell lines.

**Animal Models**

Another critical tool for both understanding the characteristics of a pathogen, the response to it, and for the development of effective therapeutics is the use of animal model systems. Animal systems allow a more wholistic simulation of the biological processes involved in infection compared to laboratory models. Here, too, however, the requirement for BSL-3 laboratory facilities for live infection studies has hampered the ability to do large scale animal research. The availability of non-human primates, including rhesus macaques, for large-scale and high-quality SARS-CoV-2 challenge experiments for therapeutics and prophylaxis remains a challenge.

**CLINICAL TRIAL DESIGN**

Large-scale, well-designed, controlled trials are the gold standard and an essential tool to evaluate any therapeutic intervention, no matter the context. Clinical trials run in three phases, with increasing population sizes; Phase 1 evaluates only the safety with a small population of patients; Phase 2 increases the study population to several hundred and looks both at the safety and early evidence of potential efficacy of the intervention; finally, Phase 3 trials have a larger sample size and can therefore directly compare the intervention to placebo/no treatment (or other treatments) in an unbiased manner. To increase efficiency in the context of a public health emergency, several COVID-19 clinical trials are running seamlessly between these phases along a master protocol determined at the trial initiation.
Clinical trials for drug development typically are designed by pharmaceutical companies running the trials themselves. However, when facing a public health crisis, centralized guidance and coordination of these trials is essential, as this provides structure that allows for the establishment of multiple lines of actions for the various circumstances in which treatments could be provided and also allow for cross-product evaluation. Clinical trials are time-consuming and can be costly, thus, care must be taken at the outset to ensure this investment results in high quality data that immediately inform clinical decisions. This requires rigorously designed studies that are adequately powered, meticulously implemented, and that aim for high retention of participants. In addition, it is critically important that clinical trials be conducted among diverse populations, particularly groups most severely impacted by COVID-19. Over the course of the COVID-19 pandemic, the US has fallen behind much of the world in its ability to coordinate, mount, run, and evaluate clinical trials in order to accelerate identification of effective treatments, and this must be rectified.

Adaptive Trial Design and Platform Clinical Trials

There has been some use of adaptive trial design, a clinical trial design which promises to rapidly improve the understanding and availability of COVID-19 treatments; and expanding the use of this design should be a priority. In adaptive trial design, the results of a study can alter – mid-course – the design parameters, the control groups, the comparisons between interventions, and the endpoints of other ongoing studies. The utilization of these types of trials can be particularly helpful in a pandemic, in which designing, implementing, and analyzing the results of clinical studies must be nimble and prompt.

There are several examples of studies conducted outside the US that demonstrate the benefits of deploying the adaptive trial design strategy. It would allow us to immediately tailor trials to ask the most essential questions, such as comparing two therapies head-to-head or in combination.

Additionally, adaptive trial design would accelerate clinical research and allow us to save significant resources. By being able to simultaneously run multiple arms of a study against one controlled group, more significant data could be rapidly gathered with fewer overall study participants. These trials would also compare directly between potential therapeutic options – and even allow for combinations of therapies – and give information about why one candidate may be more efficacious than another. When different studies evaluate different therapeutics, it can become impossible to compare across methodologies and statistical analyses to determine which therapy is the best for each type of patient.

The public platform in the US for therapeutic clinical trials—Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)—has invested in adaptive platform clinical trials for some but not all therapeutics for COVID-19. These trials must be expanded and strengthened.
Recruitment of Diverse Trial Participants

Clinical trials depend on securing the sustained participation of volunteers in the research. Historically, there have been limitations in the types of study participants recruited and included in clinical trials, which can lead to biases in the findings from studies and create challenges in the ultimate uptake of therapeutics across population groups. If a drug is tested only on white healthy men over 60 year of age, for example, it’s unclear how it might work for a younger person, a woman, or people from different racial or ethnic backgrounds or those with co-morbid conditions.

There are barriers to recruitment of many populations in the US, including a historical and justifiable mistrust of the biomedical infrastructure among people of color, immigrants, and queer people, that continue to affect diversity in clinical trials, including those for COVID-19. But, with concerted effort and appropriate community engagement, some of these barriers can be overcome, as has been seen in the case of some of the clinical trials for COVID-19 vaccines. These studies have recruited tens of thousands of participants in the US and abroad for the largest and most rapid Phase 3 trials recorded to date, and, in the case of the Pfizer and Moderna trials in the US, have included meaningful numbers of at-risk participants from various age, racial, ethnic groups. Additional efforts are underway to recruit people of different gender identities in future vaccine trails. Much more needs to be done to engage diverse communities in all phases of research, as is noted below.

RECOMMENDATIONS:

1. NIH should develop an integrated plan, including public and private partnerships, that aims to develop small molecule therapeutics.

2. NIH and other funders should fund large, adaptive trials for COVID-19 therapeutics, including those that allow for adding or removing arms. Promising therapeutics should be immediately included onto these pre-existing trials.

3. NIH and other funders should ensure that studies of similar therapies, such as different monoclonal antibodies, are compared head-to-head in the initial clinical trials (to aid in implementation).

4. NIH and other funders should ensure that clinical trial protocols are centrally coordinated to promote comparison between the findings from various trials.

5. NIH and other funders should ensure that clinical trial recruitment focuses on diverse patient populations with attention to demographic characteristics and disease-stage.
4. BEHAVIORAL AND SOCIAL SCIENCE

SARS-CoV-2 (like HIV) is a virus that is transmitted between individuals in the course of human relationships that take place in social and environmental context. A comprehensive COVID-19 response must, therefore, include evidence not only from basic biomedical science, drug discovery, and clinical research, but also from behavioral and social science relevant to the development and deployment of both pharmaceutical and non-pharmaceutical interventions. A host of issues about human behavior, social connectedness, effective communications, and ethical policy remain to be fully explored.

THREAT PERCEPTION AND BEHAVIORAL CHOICES

Perceptions about the threat – or lack thereof – of becoming infected, getting seriously ill, and/or dying from COVID-19 is a major determinant of human behavior. Risk perception is driven by knowledge, but also, and sometimes even more so, by emotion — either fear or optimism or a combination of both. Risk perception informs the decision rules that people employ as they attempt to navigate their everyday lives including in the face of COVID-19. People calculate relative risks (e.g., is it safer to go to a store to buy food or pick up takeaway from a restaurant?), consider adapting certain behaviors (should I wear a mask or not; and, if I do, what kind?), and determine acceptable tradeoffs (if I don’t hug Grandma when I see her, is that worse for her psychologically than fear of contracting COVID?) based on some algorithm of risk. How they develop their personal algorithms is not entirely clear.

Because COVID-19 is a transmissible disease, risk fundamentally has to do with how individuals come in contact with one another. With the high level of asymptomatic infection in the population, people must assess their own risks with respect to both transmission (I may be a carrier without me knowing it) and acquisition (I could catch the disease from anyone). Since the beginning of shelter-in-place policies, the shutting of most social venues (stores, restaurants, bars, schools, gyms, etc.), and the promotion of physical distancing (unfortunately under the rubric of “social distancing”), levels of social isolation and loneliness have increased precipitously.

As a mode of coping, many individuals and families have created “pandemic pods” or “bubbles”—sets of other individuals with whom they interact based on shared agreements about not interacting with others outside their group and being vigilant about observing public health protocols (handwashing/sanitizing, mask-wearing, staying 6-feet away from others). These provide much-needed human connection, but their safety is predicated on everyone complying with the agreements and trusting that they have sufficient knowledge about any outside-the-group interactions. Underlying this whole arrangement is the sense that group members can make an accurate risk assessment from which their behavioral choices ensue. But when opportunities arise to introduce new risks – such as
opening schools for some children or allowing indoor dining in restaurants at some level of capacity—agreements and assessments have to be renegotiated in the face of more unknowns about potentially exponential contacts and exposures. How these decisions are made by individuals and groups is an area in need of further research. Learning more about this will inform our ability to develop helpful decision tools that can be flexible to respond to new scientific and policy information and adaptive for different contexts. Such decisions will remain complex even when vaccines become available and uptake of vaccines progresses differentially across subpopulations.

**SOCIAL CONTEXT**

Individual risk perception and decisions about behavioral actions are very much affected by the social and cultural context in which people live. The core elements of social context—norms, values, networks, structures, and institutions—are not fixed but change and evolve over time and reflect social inequalities and power relations. Understanding how these dynamic elements are structured, reproduced, challenged, and modified by people, and with what effects in the context of COVID-19, is essential for developing appropriate and effective pandemic mitigation and elimination strategies—diagnostic, therapeutic, and preventive—including the messaging of them. Knowledge gleaned during this pandemic likely will be applicable to future ones.

**Norms and identities**

From the broad literature on social norms, we have learned that people’s conformity to these norms may be based on a desire both to learn from others and to gain social connection and approval. Thus, people’s behavioral choices and actions with respect to COVID-19 prevention are most likely to be influenced by the norms of the communities with which they identify. There is some research that suggests that a significant level of intervention effect may come not from direct participation in an intervention, but rather from indirect effects on people’s social contacts who adopted the intervention behavior. This has implications for how COVID-19 prevention messaging might best be framed (e.g., “members of your community believe/behave . . .”). Unfortunately, as we have seen during the COVID-19 pandemic, this can work both ways, depending on the scientific and public health veracity of the message.

Moreover, much is dependent on the specific social identities people have. These can be defined by demographic characteristics (e.g., race, ethnicity, gender, age, class, geographic location) or by (often overlapping) cultural characteristics (religion, familism, politics), or, more likely, a combination of these. If being together with one’s multi-generational family on a regular basis is reflective of one’s core social identity, being told by officials to not do so may not resonate.
When making decisions about how to behave in one’s personal and social life, most people look for guidance from trusted leaders\(^81\). In the case of COVID-19, where information and public health messaging are constantly changing and are deeply politicized and where different trusted leaders—e.g., public health officials versus religious leaders—recommend different things, this is not straightforward.

**The dynamics of uncertainty and misinformation**

Since COVID-19 emerged in early 2020, communications about its spread, prevention, and impact have been central to the response everywhere. In the US (and elsewhere) it has been clear that the absence of a unified, science-based, public-health-driven message from the national leadership has significantly exacerbated the epidemic’s spread. While politics has driven much of this, the level of uncertainty surrounding the novel pathogen and its trajectory also has contributed significantly and is a key component of the current social context.

Uncertainty and evolution of knowledge are core realities in science, and it is important to know how lay people understand what these mean and how they operate within them\(^82\). “Public understanding of science” as an area of social research, examines how lay publics receive scientific knowledge and incorporate it into their everyday lives and actions and with what consequences\(^83\). For COVID-19, both the nature of the scientific knowledge and the ways in which it has been communicated to the public are complex and problematic. For example, from the beginning of the pandemic, the US President claimed the virus was a mild, flu-like disease that would “disappear” in short order; that it was intentionally foisted on the US and other countries by China (repeatedly calling it “the China virus”); and that concerns being expressed by public health scientists and clinicians about its dangerous spread were unfounded. This allowed for the growth of conspiracy theories and misinformation, exacerbated by currently available social media platforms. Simultaneously, public health officials and infectious disease experts were shouting the alarm, but, because of the uncertainty of the novel coronavirus and concerns about its potential impact on the health care system, their messages about the benefits of mask-wearing and the permissible level of social interaction changed over time.

The high level of uncertainty, inconsistent messaging, mis(or dis)information, and political polarization surrounding COVID-19 affect not only the kinds of risk perceptions and behavioral decision-making noted above, but also affect people’s willingness to participate in clinical trials of drugs and vaccines and to use the products of those trials should they prove efficacious. As such, the high uptake of vaccines in particular, which is necessary to truly put a dent in the pandemic, will require enhanced efforts to combat “vaccine hesitancy” and promote “vaccine confidence”\(^84\). It also may involve using “cognitive inoculations” to counter growing misinformation\(^85\). These efforts are complicated by structural inequalities in health and illness and historical and contemporary examples of biomedical racism, sexism, homophobia, and transphobia\(^86\).
Inequality—Pre-existing Social Conditions

The documented, disparate impact of COVID-19 on communities of color and essential workers in the US lays bare the structures of inequality in our society. While much has been written about the overlap between race, ethnicity, age, class and pre-existing medical conditions (e.g., diabetes, heart disease, respiratory illnesses) as these increase COVID-19 susceptibility, morbidity, and mortality, less has been documented about "pre-existing social conditions" that similarly are implicated. These are typically referred to in the literature as the “social determinants of health”87, meaning the core social processes and arrangements—reflective of social and cultural norms, values, networks, structures and institutions—that operate around and in concert with individuals’ behaviors and practices to influence health outcomes76.

There is evidence that social processes of racism, e.g., daily micro- (and sometimes macro-) aggressions felt by people of color, contribute to stress that then leads to other medical conditions such as high blood pressure88 that increases risk for COVID-19 (and other illnesses). Such processes, along with historical experiences of communities of color, also lead to mistrust of medical systems and public health officials89. This may render members of these communities wary about health information they receive, as the motives behind this information may be suspect to them. As a result, they may be less willing than others to adopt safety measures and more prone to conspiracy theories90. All this is exacerbated by the highly polarized and racialized political climate in which COVID-19 has emerged. There is a need for targeted public health information delivered by trusted community leaders and organizations internal to these communities, in partnership with local and national public health officials.
RECOMMENDATIONS:

1. NIH should support rapid research on how individuals, social networks, and communities devise decision rules for how they engage with others during COVID-19. Relevant questions include:
   - What kinds of algorithms, based on what inputs from which sources do people construct for making behavioral decisions, such as wearing masks, limiting social interactions, quarantining, traveling, testing, etc.?
   - How is this done in a context of uncertainty, as information (both scientific and policy-related) is constantly evolving and changing?
   - Are there extant, user-friendly, decision tools (e.g., from other infectious disease outbreaks) —that can be modified and used for COVID-19 to understand uptake of non-pharmaceutical and testing interventions?

2. NIH should support rapid research on from where and from whom people get clues about what to do in response to COVID-19 and how this becomes internalized to affect behaviors. Relevant questions include:
   - How do people balance conflicting norms/identity-based values?
   - What is the role of social media?
   - What are the most productive ways to frame public health messages in different communities that can be delivered by trusted leaders?

3. NIH and other funders should support research to identify best practices for balancing acknowledgment and respect for the lived experiences and shared concerns of communities with evidence-based public health information to facilitate health-promoting practices among these communities.

4. NIH and other funders should support robust health communications research to determine what tools exist to mitigate vaccine hesitancy and promote vaccine confidence that can be adapted for COVID-19, and to identify efficacious strategies for combating and debunking health-related conspiracy theories and misinformation in light of the impact of social media.

5. NIH and other funders should rapidly support the development of a national behavioral monitoring tool to gather insights about what is driving behavioral change in response to COVID-19 over time. This could be a periodic, cross-sectional survey to allow for rapid and adaptive monitoring of core variables related to demographics, preventive behaviors, knowledge, risk perception, trust, and stigma.
5. IMPLEMENTATION SCIENCE

Even in the short amount of time in which health care providers have treated COVID-19 cases, progress has been made in understanding how to manage patients, leading to a reduction in COVID-19 related morbidity and mortality. While development of therapeutic drugs and prevention tools is essential to further improve our ability to prevent transmission as well as prevent death and serious illness, continued improvement also is needed to better understand how to optimize the uptake and adherence with various vaccines, diagnostics, and treatments as they become available. Already, the complexity of delivering one or more vaccines to people around the world is becoming clear, based on nature of the current, promising products. A host of logistical issues related to manufacturing capacity, supply chain, cold storage requirements, multiple dosing regimens are compounded by social and economic issues related to prioritizing vaccine recipients while ensuring equity in access, combating vaccine hesitancy (and “anti-vax” campaigns), and cost and coverage.

Implementation science provides opportunities to systematically study and address many of these complex issues in the response to COVID-19. It is defined as “the study of methods for improving the uptake, implementation, and translation of research findings into routine and common practice.” It can help to better understand how to deliver the right interventions for the control of the pandemic, how to scale up delivery of prevention, diagnostic, and treatment interventions, and how to adapt to the disruption in health services as a result of the pandemic. It also is important for assessing both the direct and the indirect impact of the COVID-19 pandemic on individual and population health and health care systems.

Studies of the direct impact of COVID-19 on public health interventions are under way. For example, a study published in June 2020 assessed the implementation of physical distancing approaches by state public health agencies, finding that initiation time was shorter in decentralized agencies in comparison to those that were centralized. Additional implementation studies can help identify more precise strategies for physical distancing approaches that can be applied by localities and institutions. Finally, comparative effectiveness and cost effectiveness studies to determine optimal testing regimens and algorithms in different settings will be important to inform real world testing protocols in workplaces, congregate settings, and schools.

Implementation studies on the indirect impact of COVID-19 include attention to the adaptation of interventions being used because of the pandemic, such as telemedicine, for non-COVID-19 health issues.
The response to COVID-19 can benefit from implementation science’s use of big data (e.g., socio-economic, geographic, and genomic data), digital technologies (e.g., mobile phone applications), artificial intelligence, and deep learning for modeling as part of its methodological repertoire.

Scaling up implementation science capacity within public health efforts is essential. For example, implementation science concepts can be applied to measure the reach of contact tracing programs that incorporate electronic health record information (e.g., viral test results). In addition, implementation science research can help in evaluating the effectiveness of various interventions in diverse populations and various settings.

Notwithstanding its obvious importance in the context of COVID-19, implementation science has received relatively little attention and limited support at NIH and elsewhere, and a greater commitment and investment in it now is critical. Because the need for and expertise in implementation science research span multiple agencies and institutions, coordination is needed at a high level to develop specific research agendas that incorporate knowledge of prevention, behavior, communications, health systems, community systems, supply chains, and digital technology.

**Preparing to deliver monoclonal antibodies (mAbs)**

One very important area of implementation science that connects to the discussion of therapeutics above is the need to translate biologics, specifically monoclonal antibodies (mAbs) for therapeutics and vaccines at a scale necessary to achieve real-world effectiveness in disease outcome and epidemic spread.

In response to viral infection, patients mount an adaptive immune response that involves raising specific antibodies against the virus\(^95\). Antibodies are Y-shaped proteins that bind to and neutralize pathogens, both during the initial infection and for months or years to come, preventing or minimizing the risk of reinfection\(^96\). Researchers around the world have identified specific antibodies that bind tightly to SARS-CoV-2 and prevent it from infecting cells\(^97\). Antibodies are already used as effective therapeutics against many autoimmune disorders\(^98\).

Most recovered COVID-19 patients have antibodies against the SARS-CoV-2 virus in their blood\(^36\). As mentioned earlier, plasma derived from their blood has been used directly, since January 2020, to treat patients with COVID-19, in order to provide them with antibodies specific to the virus\(^99\). However, recovered patients have highly variable levels of SARS-CoV-2 antibodies in their plasma, and not all antibodies against the virus are effective at preventing its binding and replication\(^36\).
Clinical trials are ongoing to evaluate the effectiveness of SARS-CoV-2 monoclonal antibodies for the prevention and treatment of COVID-19\textsuperscript{100}. However effective, antibodies for therapeutics (termed biologics) are expensive and face serious hurdles at the level of manufacturing scale-up that will hinder their widespread use. Solutions to the gaps in the supply chain and delivery system must be equally evaluated when assessing the viability of products. There has never been a monoclonal antibody used at the scale that would be required for an effective and widely available COVID-19 therapeutic. Similar to government investment in vaccine doses before even Phase 1 clinical trial results, the government should invest in and scale production of these promising therapeutics immediately.

**RECOMMENDATIONS:**

1. NIH should work with its HHS partner agencies to develop a coordinated COVID-19 implementation science research agenda with specific funding. This agenda should include:
   - Research on how best to respond to COVID-19 after vaccines become available.
   - Research on care delivery approaches using adaptive study designs that can change with the introduction of new technologies and research outcomes.
   - Investigation of the value of utilizing community systems for information dissemination, support services, testing and vaccine administration.

2. The US Government must invest in planning for a coordinated scale-up of manufacturing capabilities for mAbs to ensure that if an antibody is found to safe and effective, it could be made available to all who need it in an expeditious manner.

3. NIH and other funders should support implementation science on how best to prepare for the next pandemic.
6. COMMUNITY ENGAGEMENT

In all areas of COVID-19 research, as is true of other health research, the engagement of and with affected people, communities, and other stakeholders is critical\(^\text{101}\). Particularly in the area of HIV research, there has been a gradual accumulation of experience on what engagement means, how to effectively engage diverse stakeholders, and how context influences the effectiveness of different engagement practices\(^\text{102}\). The Council for International Organizations of Medical Sciences (CIOMS) provides detailed commentary on the need to and value of engaging research participants and communities “in a meaningful participatory process that involves them in an early and sustained manner”\(^\text{103}\).

The inclusion of patients, consumers, and advocates in research priority-setting and in the design, implementation and the dissemination of results from research brings many advantages, including:

- Increased and more rapid enrollment in clinical trials
- Strengthened adherence to trial protocols
- Improved informed consent practices
- Increased gender and racial diversity in trial enrollment
- Improved understanding and acceptance of research results
- Research priorities and investment that better reflect the needs and desires of communities

In designing and implementing clinical studies for COVID-19 prevention, diagnostics, and treatment, community engagement is crucial for success. However, such engagement should not be viewed narrowly as a tool or mechanism for supporting clinical trials by, for example, establishing a Community Advisory Board chiefly to provide input into protocols that already have been designed to answer questions of interest to researchers. Rather, community engagement should be viewed as an orientation that is built into the interventions being designed and tested. Using community-based participatory research practices, specifically, allows for person-centered research that is more aligned with the interests and needs of individuals; and it allows for a shift in focus from a disease to a whole person with lived experiences\(^\text{104}\). Given how we have seen the COVID-19 pandemic play out in various communities, this orientation is essential. For example:

- Prioritization in the development of diagnostic tools to identify SARS-CoV-2 infection requires an understanding of how people view and use testing not only as a means of detecting infection or illness, but as a means of prevention and harm reduction. Asking people what they need and want from testing can help drive diagnostic research towards the development of products that are reflective of those needs and, therefore, increase utilization.
- Improved understanding of how to educate people about and increase adherence to mitigation interventions, such as physical distancing and masking, requires a detailed understanding of how very diverse communities interact, how socio-economic factors affect the ability to
use mitigation approaches, and how people react psychologically and emotionally to such interventions. Community engagement in research will help frame the questions that require investigation and frame how such questions can be asked to get detailed and honest responses.

- The inclusions of people living with long-term sequelae of COVID-19 will assist researchers in understanding how these sequelae manifest in people and, therefore, how to design studies to better understand the prevalence of these symptoms and how to address them.

- Widespread acceptance of vaccines and other prevention tools for COVID-19 will require community engagement to better understand current views of vaccine and prevention science, how to frame messaging about vaccine and other preventive intervention use, and to build confidence within communities about the value of these new tools and products.

Community engagement in COVID-19 research must ensure representation of groups that are disproportionately affected by the virus in terms of both risk of infection and severity of illness. This includes people who are vulnerable due to:

- Racial and ethnic disparities, with Latinx, Black, and Native American communities being particularly hard hit by COVID-19.

- Economic status, with those with lower incomes at greater risk of infection and with less access to health care.

- Age, with older adults at greater risk of more severe illness.

- Job status, with essential workers (e.g. health care providers, food delivery, day care providers, teachers) at greater risk of exposure and infection.

- Co-morbidities, with such conditions as diabetes, behavioral health issues, asthma, hypertension, and obesity increasing the risk of disease severity.

**RECOMMENDATIONS:**

1. NIH should solicit two civil society representatives to be members of the ACTIV convening group.

2. NIH and NIAID should add three civil society representatives within each of the ACTIV workgroups.

3. NIH should commit to having at least two members representing civil society on each study protocol for all research areas.

4. NIH should ensure that all COVID-19 prevention and treatment research study sites have Community Advisory Boards that reflect the epidemic.

5. NIH and other funders should provide support and capacity building to community representatives participating in COVID-19 research development and implementation.
7. COORDINATING THE AGENDA

Responding to a pandemic like COVID-19 requires immediate and consistent coordination across a broad array of federal agencies. Our document primarily is focused on the research agenda at the NIH; but we recognize that a comprehensive response also includes public health research and messaging from the CDC, dynamic regulation of diagnostics and treatments by the FDA, and manufacturing, supply chain, and distribution planning from BARDA, to ensure rapid, widespread, equitable, and consistent access to pharmaceutical and non-pharmaceutical interventions. Early in the COVID-19 pandemic, well-established diagnostic tests were severely limited due to poor coordination between the FDA, the CDC, and city and state public health labs. For two months, public health officials could not track their ongoing epidemics, leading to a significantly increased mortality in the pandemic’s first months in the United States. Subsequently, the lack of central coordination has led to consistent delays in COVID-19 testing times due to insufficient health care worker PPE, supply chain issues, lab staffing shortages, and an increasingly complicated patchwork of FDA authorized tests. To this day, the CDC has yet to produce clear public guidance on how and how often to test, which tests to use, and how to interpret the data.

The situation with COVID-19 treatments shows a similar lack of coordination, with conflicting clinical trial results, shortages in remdesivir, one FDA approved treatment, and an inconsistent pipeline of drug development. The coordination and urgency with which COVID-19 vaccine research and implementation moved forward also was not matched for non-pharmaceutical interventions, such as mask wearing, social distancing, and working-from-home, where there was an absence of clear and consistent behavioral guidelines that could have saved lives. Early in the pandemic, NIH-sponsored research on the efficacy of masks (of various types) to prevent COVID-19 transmission, CDC guidelines on mask wearing, and BARDA support of mask (and other PPE) supply chains all failed to materialize.

To ensure robust facilitation and coordination of all aspects of pandemic response—from discovery research to public health implementation—a dedicated office within the federal government is necessary. It is late in the day to achieve optimal coordination for addressing COVID-19, but there still is much that such an office can do to mitigate further chaos. Going forward, this office must focus on preparedness, so that once the next pandemic arrives, it will not be too late to respond effectively.
CONCLUSION

None of us could have imagined the devastation and human loss the COVID-19 pandemic already has wrought. Finding our way out of the chaos that has characterized the US response to it will require commitment to a concerted, comprehensive, and coordinated research response to produce highly effective pharmaceutical and non-pharmaceutical interventions that can be delivered to people in rapid and equitable ways.

This document has attempted to identify salient gaps in the US government’s current SARS-CoV-2/COVID-19 research agenda that, if addressed, will bring us closer to that aim. We have highlighted areas and questions that should be attended to imminently by the NIH and its federal research partners – ideally under the auspices of a high-level coordinating office—with a view toward not just this pandemic, but pandemic preparedness altogether. For, while pandemics with novel pathogens may be rare events, the past few decades show us that they will continue to occur; and we must ensure that when they do, we are able to mobilize swiftly to protect human life and prevent another catastrophe of the order we are experiencing now.

REFERENCES


